Original Article

MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis Secondary to Cancer Therapy

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BACKGROUND: Mucositis is a significant toxicity of cancer therapy with numerous systemic sequelae. The goal of this systematic review was to update the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) Clinical Practice Guidelines for the management of mucositis. **METHODS:** The literature was reviewed systematically to identify interventions for mucositis. Studies were rated according to the presence of major and minor flaws according to previously published criteria. The body of evidence for each intervention and in each treatment setting was assigned a level of evidence based on previously published criteria. Guidelines were developed based on the level of evidence, with 3 possible guideline determinations: *recommendation*, *suggestion*, or *no guideline possible*. **RESULTS:** The guideline covers evidence from 1197 publications related to oral or gastrointestinal mucositis. Thirteen new guidelines were developed for or against the use of various interventions in specific treatment settings, and 11 previous guidelines were confirmed after aa review of new evidence. Thirteen previously established guidelines were carried over because there was no new evidence for these interventions. **CONCLUSIONS:** The updated MASCC/ISOO Clinical Practice Guidelines for mucositis provide professional health caregivers with a clinical setting-specific, evidence-based tool to help with the management of mucositis in patients who have cancer. ***Cancer* 2020;126:4423-4431**.

KEYWORDS: cancer, gastrointestinal, guidelines, mucositis, Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO), oral.

INTRODUCTION

Mucositis is a common complication of radiotherapy (RT), chemotherapy (CT), a combination of RT and CT (RT-CT), and hematopoietic stem cell transplantation (HSCT). Mucositis is characterized by erythema and ulceration of the mucosal lining of the gastrointestinal (GI) tract. Oral mucositis (OM) is associated with pain, difficulty in

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The MASCC/ISOO Mucositis Guidelines are developed to facilitate the evidence-based management of mucositis. Clinicians should also use their own judgment in making treatment decisions for individual patients. The guideline authors and the MASCC/ISOO do not guarantee or take responsibility for clinical outcomes in individual patients.

Additional supporting information may be found in the online version of this article.

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eating and swallowing, the need for enteral or parenteral nutrition, increased opioid consumption, and interruptions to cancer therapy.[1,2] In immunosuppressed patients, OM is associated with bacteremia, increased inpatient hospitalization duration, and higher 100-day mortality.[1-3] GI mucositis is associated with nausea, vomiting, diarrhea, bloating, intestinal cramping, and anal pain.[4]

Extensive research has been conducted globally to prevent, treat, or alleviate the symptoms of mucositis. To make use of the plethora of findings in an educated manner in the clinic, a systematic approach to weighing the evidence and analyzing the clinical applicability has been taken. The Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO) conducted a systematic review and first developed guidelines in 2004.[5] The systematic review identified the interventions with the strongest evidence and specified the clinical setting in which these interventions are most likely to be effective. These guidelines were updated in 2009 and 2014 by the members of the Mucositis Study Group of the MASCC/ISOO.[6,7]

Considering the tremendous growth in mucositis research since the last guideline update, the MASCC/ISOO decided to perform a new systematic review and update the clinical guidelines. The goal of this endeavor is to provide clinicians with a set of interventions for mucositis with strong evidence to support or refute their use in certain clinical circumstances.

MATERIALS AND METHODS

Our methods have been described in detail in a recent publication.[8] Briefly, a search for relevant papers indexed in the literature from January 1, 2011 to June 30, 2016 was conducted using PubMed/Web of Science/EMBASE, with publications selected for review based on clear criteria. In addition, randomized clinical trials (RCTs) published between July 2016 and June 2019 were reviewed.

Articles were reviewed by 2 independent reviewers, and data were extracted using a standard electronic form. Studies were scored for their level of evidence (LoE) based on the criteria reported by Somerfield and McCrae,[9] and flaws were listed according the criteria reported by Hadorn et al.[10] A study was considered to be well designed when no major flaws were identified according to the criteria of Hadorn et al. RCTs received the most attention, although non-RCTs were analyzed as supporting evidence. A single RCT was considered insufficient to develop a guideline.

Studies comparing an agent with placebo were considered for the efficacy analysis, which focused on 4 types of effects: mucositis severity, mucositis duration, pain severity, and pain duration. Studies comparing an agent with another active control were assessed separately.

Findings from the reviewed studies were merged with the evidence reviewed in the previous MASCC/ISOO guideline update, thus covering the entire literature. Findings were then organized into the new guideline update based on the overall LoE for each intervention. Guidelines were classified as follows: *recommendation*, *suggestion*, or *no guideline possible* (NGP). Negative guidelines were based on evidence showing lack of efficacy and not indicating that the agent is harmful.

Guidelines were based on the following clinical settings: 1) the aim of the intervention (prevention or treatment), 2) the cancer treatment modality (RT, CT, RT-CT, or high-dose conditioning therapy for HSCT), and 3) the route of administration.

Because of the large volume of literature, the project was divided into 8 sections: 1) basic oral care; 2) anti-inflammatory; 3) photobiomodulation (laser and other light therapy); 4) cryotherapy; 5) antimicrobials, coating agents, anesthetics, and analgesics; 6) growth factors and cytokines; 7) natural and miscellaneous agents; and 8) all interventions for GI mucositis. The intervention keyword list for each section is detailed in the article that provides an overview of the methods.[8]

RESULTS

The literature search identified 14,690 articles, of which 627 were retrieved for detailed evaluation. The evidence from these articles was merged with 570 articles that were included in the previous systematic reviews.[7] Taken together, the guideline covers evidence from 1197 publications. The guidelines for each section are presented below. For more detailed results, including lists of all reviewed articles, please refer to the published article for each section.[11-18]

Guidelines that are new or were changed compared with the 2014 guidelines are discussed below and appear in Table 1. Guidelines for which there was new evidence but the statements remained unchanged appear in Table 1 only. The 2014 guidelines for which there was no new evidence appear in Supporting Table 1.

TABLE 1. Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology Clinical Practice Guidelines for Oral Mucositis

Section	LoE	Guideline Statement
BOC	III	• The panel suggests that implementation of *multiagent combination* oral care protocols is beneficial for the prevention of OM during CT.
	III	• The panel suggests that implementation of *multiagent combination* oral care protocols is beneficial for the prevention of OM during H&N RT.
	III	• The panel suggests that implementation of *multiagent combination* oral care protocols is beneficial for the prevention of OM during HSCT.
	III	• No guideline was possible regarding the use of *professional oral care* for the prevention of OM in patients with hematologic, solid, or H&N cancers because of limited and inconsistent data. An expert opinion complements this guideline: Although there was insufficient evidence to support the use of professional oral care for OM prevention, the panel is of the opinion that dental evaluation and treatment as indicated before cancer therapy are desirable to reduce risk for local and systemic infections from odontogenic sources.
	III	• No guideline was possible regarding the use of *patient education* for the prevention of OM in patients with hematologic cancer during HSCT or CT because of limited and inconsistent data. An expert opinion complements this guideline: The panel is of the opinion that educating patients about the benefits of BOC strategies is still appropriate because this may improve self-management and adherence to the recommended oral care protocol during cancer treatment.
	III	• No guideline was possible regarding the *use of saline or sodium bicarbonate* rinses in the prevention or treatment of OM in patients undergoing cancer therapy because of limited data. An expert opinion complements this guideline: Despite the limited data available for both saline and sodium bicarbonate, the panel recognizes that these are inert, bland rinses that increase oral clearance, which may be helpful for maintaining oral hygiene and improving patient comfort.
	III	• The panel suggests that *CHX* not be used in the prevention of OM in patients undergoing H&N RT.
Anti-inflammatory agents	I	• The panel recommends *benzydamine* mouthwash for the prevention of OM in patients with H&N cancer receiving a moderate dose RT (<50 Gy).
	II	• The panel suggests the use of *benzydamine* mouthwash for the prevention of OM in patients with H&N cancer who receive RT-CT.
PBM	I	• The panel recommends the use of intraoral *PBM* therapy using low-level laser therapy for the prevention of OM in adult patients receiving HSCT conditioned with high-dose CT, with or without TBI, using one of the selected protocols listed in Table 2.
	II	• The panel recommends the use of intraoral *PBM* therapy using low-level laser therapy for prevention of OM in adults receiving RT to the H&N (without CT) (Table 2); safety considerations unique to patients with oral cancer should be considered.
	I	• The panel recommends the use of intraoral *PBM* therapy using low-level laser therapy for the prevention of OM in adults receiving RT-CT for H&N cancer (Table 2); safety considerations unique to patients with oral cancer should be considered. • For all PBM guidelines, it is recommended that the specific PTPs of the selected protocol will be followed for optimal therapy.
Cryotherapy	II	• The panel recommends using oral *cryotherapy* to prevent OM in patients undergoing autologous HSCT when the conditioning includes high-dose melphalan.
	II	• The panel recommends using 30 min of oral *cryotherapy* to prevent OM in patients receiving bolus 5-FU CT during the infusion of the CT.
Antimicrobials, coating agents, anesthetics, and analgesics	III	• Topical *morphine* 0.2% mouthwash is suggested for the treatment of OM-associated pain in patients with H&N cancer who receive RT-CT.
	II	• *Sucralfate* (combined topical and systemic) is not recommended for the prevention of OM-associated pain in patients with H&N cancer who receive RT.
	II	• *Sucralfate* (combined topical and systemic) is not recommended for the treatment of OM-associated pain in patients with H&N cancer who receive RT.
	II	• *Sucralfate* (combined topical and systemic) is not recommended for the treatment of OM-associated pain in patients with solid cancer who receive CT.
Growth factors and cytokines	I	• The use of *KGF-1* intravenously is recommended for the prevention of OM in patients with hematologic cancer undergoing autologous HSCT with a conditioning regimen that includes high-dose CT and TBI.
	II	• The evidence suggests that topical *GM-CSF* should not be used for the prevention of OM in patients undergoing HSCT.
Natural and miscellaneous	I	• The panel recommends against the use of *glutamine* (parenteral) for the prevention of OM in patients undergoing HSCT.
	II	• The panel suggests oral *glutamine* for the prevention of OM in patients with H&N cancer who receive receiving RT-CT. The suggestion is with caution because of the higher mortality rate seen in patients undergoing HSCT who receive parenteral glutamine.
	II	• *Honey* is suggested for the prevention of OM in patients with H&N cancer who receive treatment with either RT or RT-CT.
	III	• *Chewing gum* is not suggested for the prevention of OM in pediatric patients with hematological or solid cancer who receive CT.

Abbreviations: 5-FU, 5-fluorouracil; BOC, basic oral care; CHX, chlorhexidine; CT, chemotherapy; GM-CSF, granulocyte-macrophage colony–stimulating factor; Gy, grays; H&N, head and neck; HSCT, hematopoietic stem-cell transplantation; KGF-1, keratinocyte growth factor 1; LoE, level of evidence; OM, oral mucositis; PBM, photobiomodulation; PTPs, photobiomodulation therapy parameters; RT, radiotherapy; TBI, total body irradiation.
[a]For previous guidelines that are unchanged, see Supporting Table 1.

Basic Oral Care

Basic oral care (BOC) includes all routine actions performed by the patient or care provider to reduce the bacterial load in the oral cavity, to prevent infections, and to provide comfort. This usually involves mechanical cleaning (tooth brushing, flossing), mouthwashes to reduce bacterial build-up (bland rinses), and hydration and lubrication (applying moisturizing agents) to the oral mucosal surfaces.

In this guideline update, the guidelines on BOC were divided into 5 subtopics[11]:

1. Patient education — educational interventions designed to help patients understand the importance of oral care and to perform the recommended oral practices during cancer therapy (this class of intervention is new to the guidelines);
2. Multiagent combination oral care protocols — these protocols serve to increase the awareness of patients and staff of the importance of good oral hygiene that may lead to fewer and less severe oral complications; typically, the protocols involved recommendations with regard to the timing, frequency, and products used, which included various combinations of bland mouth rinses, toothbrushes, and flossing procedures;
3. Professional oral care — protocols delivered by dental professionals before or during cancer treatment;
4. Saline — saline rinses were compared with other types of bland rinses and chlorhexidine (CHX) rinses;
5. Sodium bicarbonate — a mouthwash of sodium bicarbonate diluted in water was compared with other bland rinses and CHX rinses; and
6. Chlorhexidine — CHX rinses were compared with placebo rinses, bland mouth rinses, and other active-agent rinses.

The literature on mixed-medication mouth rinses was reviewed but was excluded from analysis because of the heterogeneity of the ingredients.

Several suggestions were made regarding multiagent combination oral care protocols for the prevention of OM in patients during CT, RT to the head and neck (H&N), or HSCT (Table 1). Because the objective of these protocols was to increase awareness of the importance of oral hygiene and enhance compliance with routine BOC rather than test the effect of a particular agent, we were able to formulate a suggestion for each population of patients with cancer despite the relatively small number of RCTs for each patient category. Furthermore, this trend was supported by numerous comparative studies.

The suggestion against CHX for the prevention of OM in patients undergoing RT to the H&N was maintained (Table 1). To clarify, this guideline only refers to the effect of CHX on OM prevention; it does not exclude the other indications for CHX, such as prevention or treatment of oral infection. If CHX is indicated because of concurrent oral infection and OM, it is acceptable to use it for the oral infection. The new RCTs were based on another patient population (RT-CT for H&N cancer)[19] or for another aim (treatment for OM rather than prevention of OM).[20]

BOC remains an important best practice for patients undergoing cancer treatments; however, as a research area, there is limited evidence from high-quality, rigorous studies. This was confirmed when patients with cancer were grouped according to treatment. To prevent misinterpretation of the guideline, the panel expanded it with expert opinion for the following areas: professional oral care, patient education, and rinse with saline or sodium bicarbonate (Table 1). This approach was also used in the 2014 guidelines. In the current update, the phrasing differentiates between evidence-based guidelines and the panel's expert opinions.

Anti-Inflammatory Agents

A new guideline was added for benzydamine[12]: a suggestion for the prevention of OM in patients with H&N cancer receiving RT and CT (Table 1).

New data regarding other anti-inflammatory agents, such as celecoxib, irsogladine maleate, misoprostol, and rebamipide, were found. The evidence for each of these agents was insufficient to support a guideline. Actually, when the previous evidence was stratified according to the setting and mode of application for misoprostol, there were too few data to justify a positive or a negative guideline for a specific setting. Therefore, the 2014 suggestion against misoprostol mouthwash for the prevention of OM in patients with H&N cancer who received RT was reversed to NGP.

Photobiomodulation

The rapidly growing field of laser and light therapy using low-level energy to stimulate biologic responses has been named *photobiomodulation* (PBM).[21] Numerous RCTs and non-RCTs have been published about the application of PBM for the management of OM. The guideline determination was influenced by RCTs that met strict clinical and scientific criteria; however, clinical studies with lower LoE were assessed and contributed to the guideline. Studies with nonreproducible PBM therapy parameters (PTPs) were excluded from guideline determination.

The current guideline update has several new insights[13]:

1. A recommendation for the prevention of OM with intraoral PBM therapy in patients who undergo HSCT (Tables 1 and 2)[13]—the current systematic review reiterates the 2014 guidelines in this patient population and increases the range of PBM settings that may be used[22];
2. A recommendation for the prevention of OM with intraoral PBM therapy in patients with cancer who receive H&N RT (without CT) (Tables 1 and 2)—this is an upgrade of the 2014 guidelines from a suggestion to a recommendation[22];
3. A recommendation for the prevention of OM with intraoral PBM therapy in patients with cancer who receive H&N RT with CT (Tables 1 and 2)—this new guideline is based on recent evidence.

In addition to the understanding described in the guidelines above, the critical review identified several flawless studies suggesting that PBM could prevent OM in specific patient populations. These protocols are highlighted (Table 2) with a clarification that the PBM settings mentioned in these protocols should be followed exactly to optimize clinical efficacy. In other words, each of the 5 suggested protocols stands alone. Individual variations may be considered for a particular patient; however, it is unclear how this will affect the clinical outcome.

We identified several RCTs aimed at the treatment of OM in pediatric patients undergoing mixed RT/RT-CT, mixed HSCT/CT, or CT for several types of cancer. The results were promising; however, it is too early to base a guideline on these findings.

Several authors suggested that PBM may have long-term carcinogenic effects.[13,23] Recent long-term follow-up studies on patients treated with PBM for the prevention of OM showed no increase in cancer recurrence. However, the analysis of these data is challenging.[24,25] Considering the conflicting evidence from animal models regarding the effect of PBM on tumor behavior, the clinician is advised to inform patients about the expected benefits and potential risks of PBM.[23,26]

Cryotherapy

Cryotherapy results in vasoconstriction of the superficial blood vessels, thereby limiting the delivery of cytotoxic drugs to the oral tissue and reducing damage to the oral mucosa. Considering that the cooling is temporary, this treatment is only applicable for cytotoxic protocols that are delivered over a short time or for cytotoxic agents with a short half-life.

The panel identified evidence to support a recommendation guideline for 2 clinical situations (Table 1). The new evidence enhanced the LoE for HSCT and strengthened both 2014 guidelines.[18]

Antimicrobials, Coating Agents, Anesthetics, and Analgesics

New evidence was identified for the following agents: morphine (topical), sucralfate (topical/systemic), fluconazole (systemic), miconazole (topical and systemic), mucoadhesive hydrogel (topical; MuGard), polyvinylpyrrolidone (topical; Gelclair), doxepin (topical), and fentanyl (transdermal).[17] The new evidence supported the suggestion in favor of topical morphine (Table 1).[17]

New studies on sucralfate did not pertain to the clinical settings referred to in the 2014 guidelines. Accordingly, the recommendations against sucralfate for 3 clinical settings remained unchanged. A clarification was added to the guideline explaining that it refers to the combined topical application and systemic administration of sucralfate (Table 1). in contrast, a previous recommendation against the use of sucralfate for the prevention of CT-associated OM was reversed to NGP in the current guidelines. It should be noted that these guidelines do not refer to the new formulation of sucralfate that has become available (polymerized cross-linked sucralfate).

In the previous review, a suggestion was made in favor of doxepin mouthwash and for transdermal fentanyl. Considering the stringent criteria needed for a guideline and the mixed study population in some of the relevant studies, the updated guideline was changed to NGP.

The previous 2014 recommendations against Iseganan, polymyxin, tobramycin, and amphotericin B (PTA) paste; and bacitracin, clotrimazole, and gentamicin (BCoG) lozenges remain unchanged because there were no new data (see Supporting Table 1).[17]

Growth Factors and Cytokines

New evidence was identified for the following agents: keratinocyte growth factor-1, granulocyte-colony stimulating factor, granulocyte-macrophage colony-stimulating factor, epidermal growth factor, and erythropoietin.[27]

TABLE 2. Recommended Intraoral Photobiomodulation Therapy Protocols for the Prevention of Oral Mucositis[a]

Cancer Treatment Modality	Wavelength, nm	Power Density (Irradiance), mW/cm^2	Time per Spot, s	Energy Density (Fluence), J/cm^2	Spot Size, cm^2	No. of Sites	Duration
HSCT	632.8	31.25	40	1.0	0.8	18	From the d after cessation of conditioning for 5 d
	650	1000[b]	2	2.0	0.04	54-70	From the first d of conditioning to d + 2 post-HSCT (for 7-13 d)
RT	632.8	24	125	3.0	1.00	12	Entire RT course
RT-CT	660	417[b]	10	4.2	0.24	72	Entire RT course
	660	625[b]	10	6.2	0.04	69	Entire RT course

Abbreviations: CT, chemotherapy; HSCT, hematopoietic stem-cell transplantation; RT, radiotherapy.
[a]For details, see Zadik et al, 2019.[13]
[b]This involves a potential thermal effect; the clinician is advised to pay attention to the specific parameters.

The new evidence published for human recombinant keratinocyte growth factor-1 did not change the 2014 guideline for this agent (Table 1).[28]

The new data about granulocyte-macrophage colony–stimulating factor addressed a novel clinical setting; therefore, the previous guideline has not been changed (Table 1).[27]

Natural and Miscellaneous Agents

New evidence about the effects of various vitamins, minerals, and nutritional supplements on OM was assessed, including glutamine, elemental diet, zinc, supersaturated calcium phosphate rinse, vitamin E, selenium, folinic acid, and calcitriol.

A recommendation against the use of parenteral glutamine in patients who undergo HSCT for the prevention of OM was determined (Table 1).[15] The change from the 2014 guidelines was an elevation of the LoE from II to I after the publication of a well designed RCT.[29] A new suggestion was made regarding *oral* glutamine tablets in patients with H&N cancer who received RT-CT for the prevention of OM (Table 1). This guideline is based on 2 RCTs showing that a glutamine dose from 10 to 30 mg daily during RT-CT may prevent OM. This guideline for oral glutamine mentions the negative guideline for parenteral glutamine and advises caution because of the higher relapse and mortality rates reported in 1 study of patients who underwent HSCT and received parenteral glutamine.[30]

The previous suggestion made for zinc in the 2014 MASCC/ISOO guidelines for patients with H&N cancer who received RT or RT-CT was reversed in the current guidelines to NGP.[7,15,31]

In this guideline update, supersaturated calcium phosphate was included in the Natural and Miscellaneous section. Because of conflicting evidence about this mouthwash in various populations of patients with cancer, no guideline was possible.[15]

Honey, applied topically and administered systemically, has been suggested for the prevention of OM in patients with H&N cancer who received either RT or RT-CT (Table 1). Some of the RCTs had a mixed patient population (RT and RT-CT), small sample size, and different sources for the honey; therefore, only a suggestion was possible.

New evidence was identified for several natural remedies and herbs. However, it was insufficient to form a guideline (a list is available in Supporting Table 2).[15]

New evidence about saliva stimulants and artificial moistening agents was reviewed as part of this update.[15] The lubricating effect of saliva as well as the protective proteins and growth factors in saliva (epidermal growth factor and fibroblast growth factor) could promote wound healing. However, there was sufficient evidence that chewing gum is not effective for the prevention of OM in pediatric patients with hematologic or solid cancers who received with CT. Therefore, a suggestion against chewing gum was made (Table 1). This guideline does not preclude the use of chewing gum for any other purpose: saliva production, flavor, refreshment, or simply pleasure.

The previous guidelines (suggestion against) for pilocarpine and pentoxifylline in specific settings remain valid (see Supporting Table 1).[7]

All Interventions for GI Mucositis

The suggestions in favor of probiotics and hyperbaric oxygen were maintained (Table 3).[14] The 2014 guidelines

TABLE 3. Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology Clinical Practice Guidelines for Gastrointestinal Mucositis[a]

LoE	Guideline
III	The panel suggests that *probiotics containing Lactobacillus* spp. may be beneficial for the prevention of RT-induced or RT-CT–induced diarrhea in patients with pelvic malignancy.
II	The panel suggests that *hyperbaric oxygen* is an effective way to treat RT-induced proctitis in patients with pelvic malignancy.

Abbreviations: CT, chemotherapy; LoE, level of evidence; RT, radiotherapy.
[a]For previous guidelines that are unchanged, see Supporting Table 1.

in favor of amifostine, octreotide, sucralfate enemas, and sulfasalazine and the 2014 guidelines against the use of oral 5-acetyl salicylic acid and related compounds (mesalazine and olsalazine), oral sucralfate, and misoprostol suppositories in specific treatment settings were unchanged (see Supporting Table 1).

New evidence was identified for antimicrobials (ciprofloxacine and metronidazole), famotidine, a fat-modified diet, formalin, glutamine, fiber, palifermin, sodium butyrate, and steroid. Because of inadequate and/or conflicting evidence, no guideline was possible for these agents.[14]

DISCUSSION

The MASCC/ISOO guidelines for the management of mucositis are a weighted summary of the best available scientific evidence, framed in a practical clinical context. This update of the guidelines was based on an extensive, systematic review using meticulous methods that contribute to the robustness of the conclusions. Thirteen new guidelines were delineated, 11 previous guidelines were confirmed after a review of new evidence, and 13 previously established guidelines were carried over to this version because no new evidence was available for these interventions.

Some of the interventions reported in this systematic review have various formulas (eg, glutamine), may be absorbed differently, depending on the compound (eg, zinc), may be manufactured from various sources (eg, honey), or may be delivered over various time periods (eg, cryotherapy). These factors may influence the clinical outcome. To simplify the analysis and its implications the information was generalized. These differences have been clarified in the detailed articles.[11-18,27]

Furthermore, some of the interventions may only be available in certain geographic areas (eg, certain herbal compounds) or may have different regulations determined by local drug agencies (eg, PBM). Economic challenges also may play a role in the selection of the preferred treatment. Therefore, it is clear that the application of the guidelines will need to be adjusted according to the individual clinic's considerations and patient's preference.

In the 16 years since publication of the first MASCC/ISOO Mucositis Guidelines, the landscape of mucositis research has changed.[5] Over the years, we have noticed a dramatic increase in the number of interventions studied for mucositis and in the quality of the study design used to assess the efficacy of these interventions. Our knowledge on the pathogenesis of OM has also improved.[32] Although we reviewed a large body of evidence, there are still clinical settings for which there is no recommended intervention. Until more research is available, pain relief, dietary support, and secondary infection prevention are key elements in patient management.

As the number of positive guidelines increases, it should be noted that they are not presented in order of preference. All effective interventions for the specific clinical setting described are reasonable. In addition, the guidelines do not preclude other interventions that work well in the hands of a clinician.

Evidently, the biggest step up in the search for effective therapy for mucositis was in the field of PBM.[13] The current guidelines are based on stronger evidence, address more clinical settings, and offer more PBM protocols. Although the calibration of various PBM protocols was enigmatic, we advised that each protocol be applied as a whole. Research about the principles for calibration between various wavelengths and various PTPs will open the door for many more effective PBM protocols.

Other types of mucositis have recently been reported in association with targeted therapy and immunotherapy. Although these types of mucositis meet the Medical Subject Heading definition of mucositis, they are not covered in the current set of clinical practical guidelines. A long-term OM complication of cancer therapy was recently reported called chronic OM[33] and is not addressed in this guidelines update.

The ultimate goal of these guidelines is to improve the supportive care for patients with cancer and provide directions for future trials. As new research is conducted, new evidence will become available. To this end, the Mucositis Study Group of the MASCC/ISOO plans to continue updating the guidelines periodically.

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CONFLICT OF INTEREST DISCLOSURES

According to Multinational Association of Supportive Care in Cancer (MASCC) guidelines policy, employees of commercial entities were not eligible to serve on this MASCC Guidelines Panel. Sharon Elad reports consultation fees from Falk Pharma, outside the submitted work. Rajesh V. Lalla reports institutional research support from Novartis, Oragenics, and Sucampo Pharma, outside the submitted work; grants and personal fees from Galera Therapeutics, outside the submitted work; personal fees from Alira Health, Colgate Oral Pharmaceuticals, Eagle Pharma, Enlivity, Ingalfarma SA, Meiji Seika Pharma, Monopar Therapeutics, Mundipharma, and Sucampo Pharma, outside the submitted work; stock ownership in Logic Biosciences; and has a patent pending (WO 2019/217536 A2; University of Connecticut, applicant). Deborah P. Saunders reports institutional research support from Galera Therapeutics. Paolo Bossi reports personal fees from Merck Serono, Roche, Sanofi, Merck Sharp & Dohme, Sun Pharma, AstraZeneca, Kyowa Hakko Kyrin, AstraZeneca, Bristol-Myers Squibb, Helsinn, and Glaxo-Smith-Kline, outside the submitted work. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Sharon Elad: Conception and design, collection of data, assembly of data, data analysis and interpretation, and writing, review and revision. **Karis Kin Fong Cheng:** Conception and design, collection of data, and writing, review and revision. **Rajesh V. Lalla:** Conception and design, collection of data, data analysis and interpretation, and writing, review and revision. **Noam Yarom:** Collection of data, assembly of data, data analysis and interpretation, and writing, review and revision. **Catherine Hong:** Collection of data, assembly of data, data analysis and interpretation, and writing, review and revision. **Richard M. Logan:** Collection of data, assembly of data, and writing, review and revision. **Joanne Bowen:** Conception and design, collection of data, assembly of data, data analysis and interpretation, and writing, review and revision. **Rachel Gibson:** Collection of data, assembly of data, data analysis and interpretation, and writing, review and revision. **Deborah P. Saunders:** Collection of data and writing, review and revision. **Yehuda Zadik:** Collection of data, assembly of data, data analysis and interpretation, and writing, review and revision. **Anura Ariyawardana:** Collection of data, assembly of data, data analysis and interpretation, and writing, review and revision. **Maria Elvira Correa:** Collection of data, assembly of data, data analysis and interpretation, and writing, review and revision. **Vinisha Ranna:** Conception and design, collection of data, and writing, review and revision. **Paolo Bossi:** Conception and design, collection of data, data analysis and interpretation, and writing, review and revision. All authors were accountable for all aspects of the work and approved the final version of the article.

REFERENCES

1. Sonis ST, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *J Clin Oncol*. 2001;19:2201-2205.
2. Vera-Llonch M, Oster G, Ford CM, Lu J, Sonis S. Oral mucositis and outcomes of allogeneic hematopoietic stem-cell transplantation in patients with hematologic malignancies. *Support Care Cancer*. 2007;15:491-496.
3. Elting LS, Cooksley C, Chambers M, Cantor SB, Manzullo E, Rubenstein EB. The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. *Cancer*. 2003;98:1531-1539.
4. Keefe DM, Gibson RJ, Hauer-Jensen M. Gastrointestinal mucositis. *Semin Oncol Nurs*. 2004;20:38-47.
5. Rubenstein EB, Peterson DE, Schubert M, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer*. 2004;100:2026-2046.
6. Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer*. 2007;109:820-831.
7. Lalla RV, Bowen J, Barasch A, et al. MASCC/ISOO Clinical Practice Guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 2014;120:1453-1461.
8. Ranna V, Cheng KKF, Castillo DA, et al. Development of the MASCC/ISOO clinical practice guidelines for mucositis: an overview of the methods. *Support Care Cancer*. 2019;27:3933-3948.
9. Somerfield MR, McCrae RR. Stress and coping research. Methodological challenges, theoretical advances, and clinical applications. *Am Psychol*. 2000;55:620-625.
10. Hadorn DC, Baker D, Hodges JS, Hicks N. Rating the quality of evidence for clinical practice guidelines. *J Clin Epidemiol*. 1996;49:749-754.
11. Hong CHL, Gueiros LA, Fulton JS, et al. Systematic review of basic oral care for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer*. 2019;27:3949-3967.
12. Ariyawardana A, Cheng KKF, Kandwal A, et al. Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer*. 2019;27:3985-3995.
13. Zadik Y, Arany PR, Fregnani ER, et al. Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer*. 2019;27:3969-3983.
14. Bowen JM, Gibson RJ, Coller JK, et al. Systematic review of agents for the management of cancer treatment-related gastrointestinal mucositis and clinical practice guidelines. *Support Care Cancer*. 2019;27:4011-4022.
15. Yarom N, Hovan A, Bossi P, et al. Systematic review of natural and miscellaneous agents for the management of oral mucositis in cancer patients and clinical practice guidelines-part 1: vitamins, minerals, and nutritional supplements. *Support Care Cancer*. 2019;27:3997-4010.
16. Yarom N, Hovan A, Bossi P, et al. Systematic review of natural and miscellaneous agents, for the management of oral mucositis in cancer patients and clinical practice guidelines—part 2: honey, herbal compounds, saliva stimulants, probiotics, and miscellaneous agents. *Support Care Cancer*. 2020;28:2457-2472.
17. Saunders DP, Rouleau T, Cheng K, et al. Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer*. 2020;28:2473-2484.
18. Correa MEP, Cheng KKF, Chiang K, et al. Systematic review of oral cryotherapy for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer*. 2020;28:2449-2456.
19. Diaz-Sanchez RM, Pachon-Ibanez J, Marin-Conde F, Rodriguez-Caballero A, Gutierrez-Perez JL, Torres-Lagares D. Double-blind, randomized pilot study of bioadhesive chlorhexidine gel in the prevention and treatment of mucositis induced by chemoradiotherapy of head and neck cancer. *Med Oral Patol Oral Cir Bucal*. 2015;20:e378-e385.
20. Roopashri G, Jayanthi K, Guruprasad R. Efficacy of benzydamine hydrochloride, chlorhexidine, and povidone iodine in the treatment of oral mucositis among patients undergoing radiotherapy in head and neck malignancies: a drug trial. *Contemp Clin Dent*. 2011;2:8-12.
21. Low-Level Light Therapy. Accessed May 19, 2020. https://www.ncbi.nlm.nih.gov/mesh/?term=photobiomodulation.2020
22. Migliorati C, Hewson I, Lalla RV, et al. Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21:333-341.
23. Sonis ST, Hashemi S, Epstein JB, Nair RG, Raber-Durlacher JE. Could the biological robustness of low level laser therapy (photobiomodulation) impact its use in the management of mucositis in head and neck cancer patients. *Oral Oncol*. 2016;54:7-14.
24. Antunes HS, Herchenhorn D, Small IA, et al. Long-term survival of a randomized phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis. *Oral Oncol*. 2017;71:11-15.
25. Brandao TB, Morais-Faria K, Ribeiro ACP, et al. Locally advanced oral squamous cell carcinoma patients treated with photobiomodulation for prevention of oral mucositis: retrospective outcomes and safety analyses. *Support Care Cancer*. 2018;26:2417-2423.
26. de Pauli Paglioni M, Araujo ALD, Arboleda LPA, et al. Tumor safety and side effects of photobiomodulation therapy used for prevention and management of cancer treatment toxicities. A systematic review. *Oral Oncol*. 2019;93:21-28.
27. Logan RM, Al-Azri AR, Bossi P, et al. Systematic review of growth factors and cytokines for the management of oral mucositis in

cancer patients and clinical practice guidelines. *Support Care Cancer*. 2020;28:2485-2498.
28. European Medicines Agency (EMA). Kepivance. Accessed July 28, 2019. https://www.ema.europa.eu/en/medicines/human/EPAR/kepivance
29. Uderzo C, Rebora P, Marrocco E, et al. Glutamine-enriched nutrition does not reduce mucosal morbidity or complications after stem-cell transplantation for childhood malignancies: a prospective randomized study. *Transplantation*. 2011;91:1321-1325.
30. Pytlik R, Benes P, Patorkova M, et al. Standardized parenteral alanyl-glutamine dipeptide supplementation is not beneficial in autologous transplant patients: a randomized, double-blind, placebo controlled study. *Bone Marrow Transplant*. 2002;30:953-961.
31. Yarom N, Ariyawardana A, Hovan A, et al. Systematic review of natural agents for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21:3209-3221.
32. Bowen J, Al-Dasooqi N, Bossi P, et al. The pathogenesis of mucositis: updated perspectives and emerging targets. *Support Care Cancer*. 2019;27:4023-4033.
33. Elad S, Zadik Y. Chronic oral mucositis after radiotherapy to the head and neck: a new insight. *Support Care Cancer*. 2016;24:4825-4830.