

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

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**BACKGROUND:** Mucositis is a highly significant, and sometimes dose-limiting, toxicity of cancer therapy. 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 mucositis. **METHODS:** A literature search was conducted to identify eligible published articles, based on predefined inclusion/exclusion criteria. Each article was independently reviewed by 2 reviewers. Studies were rated according to the presence of major and minor flaws as per previously published criteria. The body of evidence for each intervention, 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 literature search identified 8279 papers, 1032 of which were retrieved for detailed evaluation based on titles and abstracts. Of these, 570 qualified for final inclusion in the systematic reviews. Sixteen new guidelines were developed for or against the use of various interventions in specific treatment settings. In total, the MASCC/ISOO Mucositis Guidelines now include 32 guidelines: 22 for oral mucositis and 10 for gastrointestinal mucositis. This article describes these updated guidelines. **CONCLUSIONS:** The updated MASCC/ISOO Clinical Practice Guidelines for mucositis will help clinicians provide evidence-based management of mucositis secondary to cancer therapy. *Cancer* 2014;000:000-000. © 2014 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

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

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

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**Disclaimer:** The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) Mucositis Guidelines are developed to facilitate the evidence-based management of mucositis. However, 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.

These guidelines refer to the use of the listed agents for the specific indication listed (ie, the prevention or treatment of mucositis or related symptoms). These guidelines do not apply to the use of the listed agents for other indications. For example, although it is suggested that chlorhexidine mouthwash not be used to prevent oral mucositis in patients receiving head and neck radiation therapy, clinicians may choose to use this agent for other indications in this or other populations.

**DOI:** 10.1002/cncr.28592, **Received:** September 12, 2013; **Revised:** November 21, 2013; **Accepted:** December 20, 2013, **Published online** Month 00, 2014 in Wiley Online Library (wileyonlinelibrary.com)

## INTRODUCTION

Mucositis refers to mucosal damage secondary to cancer therapy occurring in the oral cavity; pharyngeal, laryngeal, and esophageal regions; and other areas of the gastrointestinal tract. Mucositis can be caused by chemotherapy and/or radiation therapy. It occurs in approximately 20% to 40% of patients receiving conventional chemotherapy, 80% of patients receiving high-dose chemotherapy as conditioning for hematopoietic stem cell transplantation (HSCT), and nearly all patients receiving head and neck radiation therapy (H&NRT).<sup>1-3</sup> Oral mucositis presents as erythema and/or ulceration of the oral mucosa. In addition, the pharyngeal, laryngeal, and esophageal mucosa are also at risk for mucositis, particularly in patients undergoing H&NRT. It is typically very painful, requiring opioid analgesics, and impairs nutritional intake and quality of life.<sup>4,5</sup> Gastrointestinal mucositis presents with debilitating symptoms such as pain, nausea/vomiting, and diarrhea.<sup>6</sup> Severe mucositis can necessitate a reduction in the chemotherapy dose or a treatment break in RT, which can negatively influence prognosis.<sup>7,8</sup> In addition, mucositis has a considerable economic impact, due to costs associated with symptom management, nutritional support, management of secondary infection, and hospitalization.<sup>7,9</sup> Thus, mucositis is a highly significant, and sometimes dose-limiting, toxicity of cancer therapy.

Although direct cell damage from chemotherapy and/or RT initiates the process, evidence suggests that the pathogenesis of mucositis is more complex.<sup>10</sup> A 5-stage model has been proposed.<sup>11</sup> Reactive oxygen species, second messengers, proinflammatory cytokines and pathways, and metabolic byproducts of colonizing microorganisms are all believed to play a role in amplifying the tissue injury.<sup>12</sup> As a result, a large number of diverse interventions have been tested for mucositis. Although many of these interventions are available over the counter or for off-label use or marketed as devices, to the best of our knowledge only 1 agent to date has been approved by the US Food and Drug Administration as a drug for mucositis, albeit in a relatively restricted population. Studies of many interventions range widely in quality, sometimes with conflicting results. Therefore, there is a need for evidence-based clinical practice guidelines for mucositis to guide clinicians on which interventions are truly effective.

In 2004, the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) published what to our knowledge were the first evidence-based clinical practice guidelines for mucositis.<sup>13,14</sup> The first update of these guidelines was published in *Cancer* in

2007.<sup>15</sup> Over the last decade, other organizations have also published guidelines for mucositis. The guidelines published by the European Society for Medical Oncology are a direct adoption of the MASCC/ISOO guidelines.<sup>16</sup> The guidelines published by the US National Comprehensive Cancer Network are an adaptation of the MASCC/ISOO guidelines, combined with expert opinion.<sup>17</sup> Thus, the MASCC/ISOO mucositis guidelines are the leading clinical practice guidelines for this toxicity. Due to the large volume of additional literature published since the last update, we undertook the second revision of these guidelines, which is presented here.

## MATERIALS AND METHODS

Our methods and the underlying considerations have been described in detail in 2 recent publications.<sup>18,19</sup> In brief, we developed evidence-based guidelines based on systematic reviews of the evidence for various interventions. A research librarian constructed search strategies and conducted literature searches through the OVID interface to Medline. Inclusion criteria were English language publications reporting testing of an intervention for mucositis in humans, published in a peer-reviewed journal, and indexed in Medline on or before December 31, 2010. We excluded articles that did not report the effects of an intervention on mucositis or mucositis-related outcomes (such as pain), animal or in vitro studies, and literature reviews. Due to the large number and diverse range of interventions, the reviewers and articles were organized into 8 clinical sections. One section focused on gastrointestinal mucositis and 7 sections examined the following classes of interventions for oral mucositis: 1) basic oral care; 2) growth factors and cytokines; 3) antiinflammatory agents; 4) antimicrobials, coating agents, anesthetics, and analgesics; 5) laser and other light therapy; 6) cryotherapy; and 7) natural and miscellaneous agents. Each of the 8 sections had a section head,  $\geq 1$  co-section heads, and 5 to 10 reviewers. All participants were calibrated to ensure consistency in the application of the review criteria. In addition, reviewers and section heads were provided with role-specific written instructions and a manual detailing the procedures. Each article was independently reviewed by 2 reviewers. Each reviewer extracted and entered up to 66 fields of data per article into an electronic reviewer form. The quality of the reviewed literature was assessed by identifying major and minor flaws as per the criteria published by Hadorn et al (see online supporting information).<sup>20</sup> These criteria specify major and minor flaws for 8 study design variables: selection of patients, allocation to groups, therapeutic regimen, study administration,

withdrawals, blinding, outcome measurement, and statistical analysis. The section heads finalized the reviews of each article and adjudicated discrepancies between the 2 reviewers. Then the overall body of evidence for each intervention, in each treatment setting, was evaluated and assigned a level of evidence, based on criteria published by Somerfield et al (Table 1).<sup>21</sup> These criteria allocate levels of evidence based on the type of study and according to whether a study is well designed. To minimize subjectivity, we defined a “well-designed study” as a study with no major flaws, as per the criteria of Hadorn et al.<sup>20</sup> The level of evidence for each intervention was then translated into a provisional guideline, based on criteria published by Somerfield et al (Table 2).<sup>21</sup> There were 3 possible categories: “recommendation,” “suggestion,” or “no guideline possible.” Level I or II evidence was required to support a recommendation, which could only be achieved by  $\geq 1$  randomized controlled trials without any major flaws. A suggestion was possible for lower-level evidence but only with consistent evidence from multiple studies and panel consensus on the interpretation of this evidence. When adequate evidence demonstrated the lack of efficacy of an agent, a guideline “against” the use of that agent was developed. The provisional guidelines were discussed and finalized at a full-day, in-person guidelines meeting attended by > 60 members of the panel and 2 independent observers.

**RESULTS**

The literature search identified 8279 articles, 1032 of which were retrieved for detailed evaluation based on titles and abstracts; of these, 570 articles qualified for final inclusion in the systematic reviews (see online supporting information). Less than 5% of all studies reviewed were determined to have no major flaws, as per the criteria of

**TABLE 2.** Criteria for Each Guideline Category

Recommendation	Reserved for guidelines that are based on level I or level II evidence.
Suggestion	Used for guidelines that are based on level III, level IV, and level V evidence; this implies panel consensus regarding the interpretation of this evidence.
No guideline possible	Used when there is insufficient evidence on which to base a guideline; this implies 1) that there is little or no evidence regarding the practice in question, or 2) that the panel lacks consensus on the interpretation of existing evidence.

Adapted from Somerfield MR, Padberg JR, Pfister DG, et al. ASCO clinical practice guidelines: process, progress, pitfalls, and prospects. *Class Pap Curr Comments*. 2000;4:881-886.<sup>21</sup>

Hadorn et al.<sup>20</sup> Summary results for each section are presented below and in Tables 3 and 4, which also list the specifics of each guideline (whether for the prevention or treatment of mucositis and the specific patient population it applies to). For more detailed results of each section, including tables listing the details of every article reviewed, please refer to the recently published articles from the individual sections.<sup>22-31</sup>

**Gastrointestinal Mucositis (Not Including the Oral Cavity)**

The previous version of the MASCC/ISOO guidelines for gastrointestinal mucositis included guidelines in favor of amifostine, octreotide, sucralfate enemas, and sulfasalazine in specific treatment settings (Table 3). In addition, it included guidelines against the use of 5-acetyl salicylic acid and related compounds and oral sucralfate. Based on the present systematic review, these prior guidelines were able to be continued with no changes. One previous guideline, which was against the use of systemic glutamine for the prevention of gastrointestinal mucositis in patients receiving standard-dose and high-dose chemotherapy, was changed to “No guideline possible,” based on the incorporation of newer evidence. In addition, 3 new guidelines were developed: 1) a suggestion in favor of hyperbaric oxygen to treat radiation-induced proctitis; 2) a suggestion for probiotic agents containing *Lactobacillus* species for the prevention of chemotherapy and radiation-induced diarrhea in patients with pelvic malignancy; and 3) a recommendation against the use of misoprostol suppositories for the prevention of acute radiation-induced proctitis (Table 3).<sup>22</sup> Due to inadequate and/or conflicting evidence, no guideline was possible for several agents reviewed, including activated charcoal, balasalazide, budesonide, cefixime, celecoxib, cholestyramine/levofloxacin, chrysin, circadian rhythm, formalin, heater probes, leucovorin, metronidazole, neomycin, palifermin, physical activity, and sodium butyrate.

**TABLE 1.** Criteria for Each Level of Evidence

I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power).
II	Evidence obtained from at least 1 well-designed experimental study; randomized trials with high false-positive and/or false-negative errors (low power).
III	Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pretest-posttest comparison, cohort, time, or matched case-control series.
IV	Evidence obtained from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies.
V	Evidence obtained from case reports and clinical examples.

Adapted from Somerfield MR, Padberg JR, Pfister DG, et al. ASCO clinical practice guidelines: process, progress, pitfalls, and prospects. *Class Pap Curr Comments*. 2000;4:881-886.<sup>21</sup>

**TABLE 3.** MASCC/ISOO Clinical Practice Guidelines for Gastrointestinal Mucositis (Not Including the Oral Cavity)<sup>a</sup>


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RECOMMENDATIONS IN FAVOR OF AN INTERVENTION (ie, strong evidence supports effectiveness in the treatment setting listed):

1. The panel *recommends* that intravenous amifostine be used, at a dose of  $\geq 340$  mg/m<sup>2</sup>, to *prevent* radiation proctitis in patients receiving radiation therapy (II).
2. The panel *recommends* that octreotide, at a dose of  $\geq 100$   $\mu$ g subcutaneously twice daily, be used to *treat* diarrhea induced by standard- or high-dose chemotherapy associated with HSCT, if loperamide is ineffective (II).

SUGGESTIONS IN FAVOR OF AN INTERVENTION (ie, weaker evidence supports effectiveness in the treatment setting listed):

1. The panel *suggests* that intravenous amifostine be used to *prevent* esophagitis induced by concomitant chemotherapy and radiation therapy in patients with non-small cell lung carcinoma (III).
2. The panel *suggests* that sucralfate enemas be used to *treat* chronic radiation-induced proctitis in patients with rectal bleeding (III).
3. The panel *suggests* that systemic sulfasalazine, at a dose of 500 mg administered orally twice a day, be used to *prevent* radiation-induced enteropathy in patients receiving radiation therapy to the pelvis (II).
4. The panel *suggests* that probiotics containing *Lactobacillus* species be used to *prevent* diarrhea in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy (III).
5. The panel *suggests* that hyperbaric oxygen be used to *treat* radiation-induced proctitis in patients receiving radiation therapy for a solid tumor (IV).

RECOMMENDATIONS AGAINST AN INTERVENTION (ie, strong evidence indicates lack of effectiveness in the treatment setting listed):

1. The panel *recommends* that systemic sucralfate, administered orally, *not* be used to *treat* gastrointestinal mucositis in patients receiving radiation therapy for a solid tumor (I).
2. The panel *recommends* that 5-acetyl salicylic acid (ASA), and the related compounds mesalazine and olsalazine, administered orally, *not* be used to *prevent* acute radiation-induced diarrhea in patients receiving radiation therapy for a pelvic malignancy (I).
3. The panel *recommends* that misoprostol suppositories *not* be used to *prevent* acute radiation-induced proctitis in patients receiving radiation therapy for prostate cancer (I).

SUGGESTIONS AGAINST AN INTERVENTION (ie, weaker evidence indicates lack of effectiveness in the treatment setting listed):

None

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Abbreviations: HSCT, hematopoietic stem cell transplantation; MASCC/ISOO, Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology.

<sup>a</sup>Level of evidence for each guideline is in brackets following the guideline statement.

## Oral Mucositis

### Basic oral care

The results of the current systematic review indicated that most studies examining the use of oral care protocols for the prevention of oral mucositis reported a beneficial effect. These protocols typically included a combination of tooth-brushing, flossing, and  $\geq 1$  mouth rinses to maintain oral hygiene. Although the evidence was not strong enough to support a recommendation, there was adequate positive evidence to support a suggestion in favor of using oral care protocols for the prevention of oral mucositis across all cancer treatment modalities (Table 4). The evidence also supported a suggestion against the use of chlorhexidine mouthwash for the prevention of oral mucositis in patients receiving H&NRT. No guideline was possible regarding the use of oral care protocols for the treatment of oral mucositis. In addition, no guideline was possible related to the individual use of the following mouth rinses: saline, sodium bicarbonate, mixed medication mouthwashes, calcium phosphate, and chlorhexidine in patients receiving chemotherapy, due to inadequate and/or conflicting evidence.<sup>31</sup>

### Growth factors and cytokines

To the best of our knowledge, palifermin (keratinocyte growth factor-1) is the only agent that has been approved as a drug by the US Food and Drug Administration and the European Medicines Agency for oral mucositis. Evidence included a large, well-designed, randomized controlled trial and other supporting studies.<sup>32</sup> The previous

version of the MASCC/ISOO guidelines for oral mucositis included a recommendation in favor of this agent for the prevention of oral mucositis in patients receiving high-dose chemotherapy and total body irradiation followed by autologous stem cell transplantation for hematological malignancies. Based on the current systematic review, this recommendation was continued with no change in the target population (Table 4). The evidence reviewed also continued to support a suggestion against the use of granulocyte-macrophage-colony-stimulating factor mouthwash for the prevention of oral mucositis in patients undergoing autologous or allogeneic HSCT. Furthermore, the use of granulocyte-colony-stimulating factor during H&NRT has been associated with reduced local tumor control.<sup>33</sup> Due to inadequate and/or conflicting evidence, no guideline was possible for the following agents reviewed: palifermin and granulocyte-macrophage-colony-stimulating factor in treatment settings other than that listed above, fibroblast growth factor-20, keratinocyte growth factor-2, granulocyte-colony-stimulating factor, transforming growth factor- $\beta$ , epidermal growth factor, milk-derived growth factor extract, interleukin-11, ATL-104, and recombinant human intestinal trefoil factor.<sup>23</sup>

### Antiinflammatory agents

Benzydamine hydrochloride is a nonsteroidal antiinflammatory drug that can inhibit the production of proinflammatory cytokines such as tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$ . The previous version of

**TABLE 4.** MASCC/ISOO Clinical Practice Guidelines for Oral Mucositis<sup>a</sup>


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RECOMMENDATIONS IN FAVOR OF AN INTERVENTION (ie, strong evidence supports effectiveness in the treatment setting listed):

1. The panel *recommends* that 30 min of oral cryotherapy be used to *prevent* oral mucositis in patients receiving bolus 5-fluorouracil chemotherapy (II).
2. The panel *recommends* that recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) be used to *prevent* oral mucositis (at a dose of 60 µg/kg per day for 3 days prior to conditioning treatment and for 3 days after transplant) in patients receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a hematological malignancy (II).
3. The panel *recommends* that low-level laser therapy (wavelength at 650 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm<sup>2</sup>), be used to *prevent* oral mucositis in patients receiving HSCT conditioned with high-dose chemotherapy, with or without total body irradiation (II).
4. The panel *recommends* that patient-controlled analgesia with morphine be used to *treat* pain due to oral mucositis in patients undergoing HSCT (II).
5. The panel *recommends* that benzydamine mouthwash be used to *prevent* oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy (I).

SUGGESTIONS IN FAVOR OF AN INTERVENTION (ie, weaker evidence supports effectiveness in the treatment setting listed):

1. The panel *suggests* that oral care protocols be used to *prevent* oral mucositis in all age groups and across all cancer treatment modalities (III).
2. The panel *suggests* that oral cryotherapy be used to *prevent* oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for HSCT (III).
3. The panel *suggests* that low-level laser therapy (wavelength around 632.8 nm) be used to *prevent* oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer (III).
4. The panel *suggests* that transdermal fentanyl may be effective to *treat* pain due to oral mucositis in patients receiving conventional or high-dose chemotherapy, with or without total body irradiation (III).
5. The panel *suggests* that 2% morphine mouthwash may be effective to *treat* pain due to oral mucositis in patients receiving chemoradiation for head and neck cancer (III).
6. The panel *suggests* that 0.5% doxepin mouthwash may be effective to *treat* pain due to oral mucositis (IV).
7. The panel *suggests* that systemic zinc supplements administered orally may be of benefit to *prevent* oral mucositis in oral cancer patients receiving radiation therapy or chemoradiation (III).

RECOMMENDATIONS AGAINST AN INTERVENTION (ie, strong evidence indicates lack of effectiveness in the treatment setting listed):

1. The panel *recommends* that PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and neck cancer (II).
2. The panel *recommends* that iseganan antimicrobial mouthwash *not* be used to *prevent* oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II), or in patients receiving radiation therapy or concomitant chemoradiation for head and neck cancer (II).
3. The panel *recommends* that sucralfate mouthwash *not* be used to *prevent* oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (I) or concomitant chemoradiation (II) for head and neck cancer.
4. The panel *recommends* that sucralfate mouthwash *not* be used to *treat* oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (II) for head and neck cancer.
5. The panel *recommends* that intravenous glutamine *not* be used to *prevent* oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II).

SUGGESTIONS AGAINST AN INTERVENTION (ie, weaker evidence indicates lack of effectiveness in the treatment setting listed):

1. The panel *suggests* that chlorhexidine mouthwash *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and neck cancer (III).
2. The panel *suggests* that granulocyte-macrophage-colony-stimulating factor mouthwash *not* be used to *prevent* oral mucositis in patients receiving high-dose chemotherapy, for autologous or allogeneic stem cell transplantation (II).
3. The panel *suggests* that misoprostol mouthwash *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and neck cancer (III).
4. The panel *suggests* that systemic pentoxifylline, administered orally, *not* be used to *prevent* oral mucositis in patients undergoing bone marrow transplantation (III).
5. The panel *suggests* that systemic pilocarpine, administered orally, *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and neck cancer (III), or in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II).

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Abbreviations: Gy, grays; HSCT, hematopoietic stem cell transplantation; MASCC/ISOO, Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology; mW, milliwatt; nm, nanometers.

<sup>a</sup> Level of evidence for each guideline is in brackets after the guideline statement.

the MASCC/ISOO mucositis guidelines included a recommendation for the use of benzydamine mouthwash to prevent oral mucositis in patients with head and neck cancer who were receiving moderate-dose RT based on evidence from studies indicating a benefit in radiation doses up to 50 grays in patients not receiving concomitant chemotherapy. For the present systematic review, the entire body of evidence, including 2 additional studies in this patient population, was reviewed. These studies did not allow the extension of this recommendation to patients receiving > 50 grays of radia-

tion. A new suggestion was developed against the use of misoprostol mouth rinse for the prevention of oral mucositis in patients receiving H&NRT (Table 4). Although we reviewed 30 studies related to amifostine use for the prevention of oral mucositis in various settings, no guideline was possible due to conflicting evidence.<sup>24</sup> Additional agents reviewed for which no guideline was possible included diphenhydramine, prostaglandin E2, immunoglobulins, corticosteroids, indomethacin, azelastine, mesalazine, aspirin, orgotein, flurbiprofen, histamine, colchicine, and Placentex.<sup>25</sup>

### **Antimicrobials, coating agents, anesthetics, and analgesics**

Several topical antimicrobial agents have been examined for the treatment of oral mucositis with either negative or mixed results. The evidence reviewed supported the continuation of a recommendation against the use of lozenges containing polymyxin, tobramycin, and amphotericin and bacitracin, clotrimazole, and gentamicin as well as polymyxin, tobramycin, and amphotericin paste for the prevention of oral mucositis in patients receiving H&NRT. A new recommendation was developed against the use of iseganan mouthwash in patients receiving HSCT or H&NRT. We reviewed 20 studies examining the use of the mucosal coating agent sucralfate in various settings. The evidence supported recommendations against the use of sucralfate for the prevention or treatment of oral mucositis in patients receiving chemotherapy and also in patients receiving H&NRT. No guideline was possible for any anesthetic agent reviewed due to inadequate evidence. Guidelines were developed in favor of the use of patient-controlled analgesia with morphine, transdermal fentanyl, morphine mouth rinse, and doxepin mouth rinse for the management of oral mucositis pain in specific treatment settings (Table 4). Agents for which no guideline was possible included acyclovir, clarithromycin, nystatin, kefir, povidone-iodine, fluconazole, sodium hyaluronate topical, tetracaine, dyclonine, MGI-209 (with benzocaine), cocaine, amethocaine, capsaicin, methadone, ketamine, nortriptyline, and gabapentin.<sup>26</sup>

### **Laser and other light therapy**

We reviewed 24 studies evaluating the effects of laser or other light therapy on oral mucositis. The evidence supported the development of 2 new guidelines: a recommendation in favor of low-level laser therapy (LLLT) for the prevention of oral mucositis in patients receiving high-dose chemotherapy for HSCT with or without total body irradiation,<sup>34</sup> and a suggestion for LLLT in the prevention of oral mucositis in patients receiving H&NRT without concomitant chemotherapy (Table 4).<sup>35</sup> No guideline was possible related to the use of LLLT in any other treatment setting, or related to the use of other emerging light modalities such as light-emitting diodes and visible light.<sup>27</sup>

### **Cryotherapy**

A total of 22 eligible studies examined the placement of ice chips in the mouth during the delivery of chemotherapy. The evidence supported the continuation of a recommendation for the use of cryotherapy for the

prevention of oral mucositis in patients receiving bolus dosing of 5-fluorouracil. A suggestion for the use of cryotherapy in patients receiving high-dose melphalan as conditioning for HSCT was revised to clarify that this applies regardless of the use of concomitant total body irradiation. No guidelines related to cryotherapy were possible in other treatment settings due to inadequate evidence.<sup>28</sup>

### **Natural and miscellaneous agents**

Zinc is an essential trace element that is required for some tissue repair processes. Zinc also has an antioxidant effect. We reviewed 3 discrete studies testing zinc supplementation in patients receiving H&NRT, all of which found a positive effect. A new suggestion was developed in favor of zinc in patients with oral cancer undergoing RT or chemoradiation.<sup>36,37</sup> However, there is some evidence indicating that the use of antioxidants in smokers during H&NRT may reduce the efficacy of the RT.<sup>38</sup> The evidence reviewed supported the continuation of a recommendation against the use of intravenous glutamine for the prevention of oral mucositis in patients receiving high-dose chemotherapy for HSCT (Table 4). Due to inadequate and/or conflicting evidence, no guideline was possible in relation to other agents of natural origin reviewed, including glutamine in other treatment settings, the antioxidants vitamin A and E, honey, aloe vera, chamomile, Kamilloosan, Chinese herbals, indigowood root, manuka and kanuka oils, oral gel wafers, *Rhodiola algida*, *traumeel S*, and *Wobe-Mugos E*.<sup>29</sup>

Pilocarpine is a cholinergic agonist that stimulates salivary secretion. The present systematic review supported 2 new suggestions against the use of systemic pilocarpine specifically for the prevention of oral mucositis: during H&NRT and in patients receiving high-dose chemotherapy, with or without total body irradiation, before HSCT (Table 4). It should be noted that these guidelines apply only to the use of pilocarpine for the prevention of mucositis. Pilocarpine can be beneficial to increase salivary flow, particularly in patients treated with H&NRT who are experiencing hyposalivation. The evidence also supported the continuation of a suggestion against the use of the phosphodiesterase inhibitor pentoxifylline for the prevention of oral mucositis in patients undergoing bone marrow transplantation. Due to inadequate and/or conflicting evidence, no guideline was possible in relation to other miscellaneous agents/modalities reviewed including allopurinol, midline mucosa-sparing radiation blocks, payayor, timing of RT, bethanechol, chewing gum, propantheline, and tetrachlorodecaoxide.<sup>30</sup>

## DISCUSSION

To ensure consistency in the application of review criteria and guideline development, we reviewed the entire body of evidence for each intervention, not just the new publications since the last guidelines update. Our methodology provides confidence that the evaluation of the literature and subsequent guidelines development across various interventions are based on uniform and transparent criteria. The present systematic review resulted in the development of 16 new guidelines for or against the use of various interventions in specific treatment settings. Thus, the clinical usefulness of these guidelines should continue to increase. However, it is recognized that there are many clinical situations faced by the practitioner that are not addressed by these guidelines, due to inadequate and/or conflicting evidence. This constitutes a limitation of such strictly evidence-based guidelines. Therefore, symptom management (such as pain control and nutritional support) continues to be an important part of any mucositis management strategy.

An important new guideline developed in the present update is the new recommendation (based on level II evidence) in favor of LLLT for the prevention of oral mucositis in patients receiving HSCT conditioned with high-dose chemotherapy. In addition, a new suggestion (based on level III evidence) was developed in favor of LLLT for the prevention of oral mucositis in patients undergoing H&NRT, without concomitant chemotherapy. However, patients now typically receive H&NRT with concomitant chemotherapy, and no guideline was possible in that population due to inadequate evidence. Although the majority of studies of LLLT demonstrate a benefit, the variable quality of the studies and the wide variation in laser parameters used complicates the evaluation of the evidence.<sup>27</sup> Animal studies indicate that LLLT promotes wound healing and has an antiinflammatory effect.<sup>39,40</sup> Barriers to the acceptance of this technology include the cost of laser equipment and the labor-intensiveness of this modality (because many regimens involve the daily treatment of patients). In addition, a modality such as LLLT can only act on mucosa by direct contact. It will not be useful for areas such as pharyngeal, laryngeal, or esophageal mucosa, which are also at risk of mucositis in patients receiving H&NRT, but are difficult to directly access.

Sucralfate is a generically available mucosal coating agent. We reviewed 20 studies that clearly demonstrated a lack of benefit for sucralfate in the prevention or treatment of oral mucositis secondary to chemotherapy or RT.<sup>26</sup> Although it appears theoretically feasible that such

a protective coating can protect the exposed nerve endings and thus reduce pain, the data regarding sucralfate did not provide support for such a beneficial effect. Recently, several proprietary mucosal coating agents have been marketed as devices for oral mucositis. Our literature search identified only 1 eligible published study of one of these agents, on the basis of which no guideline was possible.

The goal of such clinical practice guidelines is to improve clinical outcomes by facilitating evidence-based care. To achieve this, it is important for the guidelines to be widely disseminated and, most importantly, adopted into routine practice. Strategies to facilitate guidelines uptake can include open-access publication of the guidelines-related articles and translations into other languages, as well as online resources, including a version suitable for viewing on a smartphone. MASCC/ISOO is also in discussions with relevant organizations to determine how we can work together to minimize duplication of effort and promote the clinical use of supportive care guidelines. The motto of the MASCC/ISOO is “Supportive care makes excellent cancer care possible.” In keeping with this, MASCC/ISOO is committed to enhancing the supportive care of oncology patients, with the goal of improving the patient experience and allowing for the delivery of optimal cancer treatment.

## FUNDING SUPPORT

The Guidelines Update Meeting was supported by BioAlliance Pharma and Helsinn Healthcare, SA. No honorarium or travel support was provided to the reviewers for participation in the guidelines update effort. No industry representatives attended the guidelines update meeting or participated in the guidelines update effort in any way.

## CONFLICT OF INTEREST DISCLOSURES

Dr. Lalla received grants from Evolife Laboratories and BioAlliance Pharma, as well as personal fees from iNova Pharmaceuticals, Sucampo, Cangene, and Ingalipharma outside of the current study. Dr. Elting received a grant from Helsinn Research funding for work outside of the current study. Dr. Epstein received a grant from 3M-Riker Canada for participation in a phase 3 study related to the current work. Dr. Keefe received grants from Helsinn Healthcare, GlaxoSmithKline, and Nestec for work outside of the current study. Dr. Sonis is an employee of Biomodels LLC, has acted as a consultant for Clinical Assistance Programs, acted as a member of the advisory board for Actogenix, acted as an advisor for Avaxia, acted as a biomodels consultant for BioAlliance, acted as a member of the advisory board for Galera, acted as a consultant for Izun, acted as an advisor for PolyMedix, acted as a biomodels consultant for Piramal, received fees as a founder-consultant for Inform Genomics, acted as a member of the advisory boards of Synedgen and Soligenix, acted as a member of the advisory board of and as a consultant for Pfizer, acted as a

member of the advisory board of Reata, acted as a consultant for Access, and acted as a biomodel consultant for Novartis and Merck for work outside of the current study. Dr. Sonis also holds the following patents that are broadly relevant to the current work: US Patent 6458777, US Patent 6663850, US Patent 6713463, US Patent 6841578B2, and US Patent 7297123.

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