



Development of the MASCC/ISOO clinical practice guidelines for mucositis: an overview of the methods

Vinisha Ranna¹ · Karis Kin Fong Cheng² · Daniel A. Castillo³ · Lorraine Porcello⁴ · Anusha Vaddi⁵ · Rajesh V. Lalla⁶ · Paolo Bossi⁷ · Sharon Elad⁵ · On behalf of the Mucositis Study group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO)

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Abstract

New studies and literature continue to emerge on the management of mucositis secondary to cancer therapy. The evidence-based clinical practice guidelines for mucositis were first published in 2004 and updated in 2007 and 2014 by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). The existing 2014 guidelines for mucositis are being updated in line with new literature to inform clinical practice. This paper describes the materials and methods employed for the comprehensive updates to the guidelines for managing mucositis.

Keywords Mucositis · Cancer · Cancer therapy · Guidelines · Methods · Data management · Systematic review

Introduction

The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) conducts periodic systematic reviews to update the clinical practice guidelines for the man-

agement of mucositis secondary to cancer therapy, first published in 2004 [1, 2]. The guidelines were first updated in 2007 [3] and then in 2014 [4]. Since the last update in 2014 which included literature published until December 2010, numerous studies addressing the management of mucositis have been published, which justified an update of the systematic review and of the MASCC/ISOO clinical practice guidelines for the management of mucositis. This paper describes the process and methods used for systematic review and comprehensive updates to the evidence-based mucositis guideline by the Mucositis Study Group of MASCC/ISOO in 2016–2018. The findings of this review will be published in a series of subsequent articles.

Previous papers [5, 6] published by the group set out the systematic review approach underlying the search strategies, databases used, data synthesis, and criteria for evaluation of scientific evidence and allocating the level of evidence. In the current update, similar methods have been used with some modifications. Specifically, changes are noted in the following sections below: literature searches; considerations related to the effectiveness; allocating a level of evidence and categories used to classify guidelines; logistics of the review process; and platform for online sharing. This enabled coordinating and sharing data to merge previous evidence with newly published data. This process was used to create, modify, support, or rescind clinical practical guidelines.

✉ Vinisha Ranna
Vinisha.Ranna@mountsinai.org

¹ Department of Oral and Maxillofacial Surgery, The Mount Sinai Hospital, 1 Gustave L. Levy Place, New York, NY 10029, USA

² Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

³ Edward G. Miner Library, University of Rochester Medical Center, Rochester, NY, USA

⁴ Bibby Dental Library, Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY, USA

⁵ Oral Medicine, Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY, USA

⁶ Section of Oral Medicine, University of Connecticut Health, Farmington, CT, USA

⁷ Department of Medical and Surgical Specialties, Radiological Sciences and Public Health - Medical Oncology, University of Brescia, Spedali Civili, Brescia, Italy

Approach of the systematic review

The approach of systematic review was critical in designing the methods of the review and thus guidelines updates.

The current review attempted to classify the literature on mucositis using a grading system for different study designs. This included all published studies regardless of study designs. The evidence was stratified and weighed based on the robustness of the study design and was therefore qualitative in nature. Randomized controlled trials (RCTs) had the most significant contribution. Evidence from less robustly designed studies supported or challenged the findings of the RCT. This method ensured that all possible data were considered in the guidelines development process. This was suitable considering that new techniques and interventions continue to be developed for the management of mucositis, many of which are studied in non-RCTs. If a purely quantitative approach was to be used, these studies would be missed. As the aim of the MSG is to provide a graded compilation of the strategies available for the management of mucositis, a qualitative approach was deemed the most suitable for systematic review of literature on management.

Scope of the review

Due to the broad scope of interventions for the management of mucositis, the review was divided into 9 sections, 8 interventional sections, and 1 non-interventional section (pathogenesis) as follows:

1. Basic oral care
2. Growth factors and cytokines
3. Anti-inflammatory
4. Antimicrobials, coating agents, anesthetics, and analgesics
5. Natural and miscellaneous agents
6. Cryotherapy
7. Gastrointestinal
8. Laser and other light therapy

A ninth section was dedicated to pathogenesis. This section systematically reviewed the literature about the pathogenesis of mucositis.

The GI section includes all type of interventions for GI mucositis, and the remaining sections are specific for interventions for oral mucositis. Similar categories of interventions have also been adopted by the Cochrane Group for their systematic reviews on interventions for oral mucositis.

Within this scope, the literature search followed certain inclusion and exclusion criteria.

Inclusion criteria:

1. Published clinical research papers testing an intervention for mucositis, or meta-analyses of such studies
2. English language
3. Published in a peer-reviewed journal
4. Articles on frequently used medical databases (PubMed (MEDLINE) as a basis) from January 1, 2011 until June 30, 2016
5. Human subjects, of all age groups

Exclusion criteria:

1. Papers that do not report the effects of an intervention on mucositis or on related outcomes such as mucositis-associated pain
2. Animal studies or in vitro studies
3. Papers published in a language other than English
4. Papers not studying preventive or therapeutic impact on mucositis as a primary outcome (i.e., tumor efficacy or drug reports)

Database search strategy

In order to begin the search for papers, keywords from the previous guidelines were used. These were augmented by keywords sent by members of the MSG. In addition, a call for keywords was publicly posted on the MASCC/ISOO website and society newsletters to include contributions from all members. To avoid any potential bias, generic names were requested, and for products described by trade names, the active ingredient was to be mentioned along with the disclosure of any conflict of interest. See Table 1 for the list of keywords used for this guidelines update.

Literature searches

Literature search strategies were developed with assistance from two medical research librarians.

The medical librarians developed an initial PubMed scoping search strategy for each section, which was shared with the section heads who identified additional articles not captured within the search. Using the Yale MeSH Analyzer, the librarians identified additional keywords that they sent to the section heads for consideration [7]. Once the keyword lists were confirmed, the librarians developed the final PubMed search strategy for each section. Each search strategy included similar keywords for cancer, oral anatomy, and mucositis, using a “modular” strategy to ensure that each search was conducted consistently for each section. Limits were applied to each section according to the inclusion and excluding criteria listed above.

Table 1 List of keywords used for the literature review

Basic oral care/good clinical practice	Growth factors and cytokines	Anti-inflammatory agents	Antimicrobials, coating agents, anesthetics, analgesics	Natural therapies and miscellaneous	Pathogenesis	Lasers	GI
Artificial saliva	ALD518	Amifostine	Acyclovir	Allopurinol	Bayesian network	CO ₂	AMP-18
Baking soda	Amino acids	Aminosalicylic acid	Adhesive	Aloe	Epigenetics	Diode	Dietary constituents
Bland rinse	ATL 104	Amlexanox	Alfentanil	<i>Aloe vera</i>	Gut-brain axis	GaAlAs	Dietary supplements
Calcium phosphate	Carcinoembryonic antigen cell adhesion molecule 1	Anti-inflammatory	Aluminum hydroxide	Alternative	Immunotherapy	He-Ne	Exercise
Calculus	Colony-stimulating factors	Anti-TNF	Amphotericin B	Azulene	Microarray	Infrared	Ginger
Caphosol	Cytokines	Anti-tumor necrosis factor	Analgesia	Bee	Microbiome sequencing	InGaAlP	Glucagon-like peptide-1
Caregiver education	Epidermal growth factor	Aspirin	Analgesic	Bethanechol	Microbiota	InGaAs	Glucagon-like peptide-2
Chlorhexidine	Erythropoietin	Benadryl	Antiacid	Calcium phosphate	miRNA	Laser	Herbs
Dental	Fibroblast growth factors	Benzylamine	Antibiotic	Cg53135 (fgf-20) (a protein with in vitro mitogenic activity on epithelial and mesenchymal cells)	Model	LED	Inulin
Dental care	Ghrelin	Betamethasone	Anti-infective	Chamomile	mTOR	Light therapy	Laxative
Dental cleaning	Glucagon-like peptide 2	Celecoxib	Aqua oral	Chewing gum	Neuroimmune	Light-emitting diode	Microbiome sequencing
Dental floss	Glutathione	Corticosteroid	Benzocaine	Chinese medicine	Personalized	Low-level laser therapy	Oxycodone-naloxone
Dentist	Granulocyte colony-stimulating factor	Dexamethasone	Buprenorphine	Clonidine	Pharmacogenetics	Low-level laser therapy	Peppermint
Education	Granulocyte-macrophage colony-stimulating factor	Diphenhydramine	Clarithromycin	Complementary	Pharmacogenomics	Photobiomodulation	Prebiotics
Family education	Hepatocyte growth factor	Ethylol	Clonidine	Curcumin	Precision	Phototherapy	Probiotics
Flossing	IL-11	Flurbiprofen	Coating agent	Doxepin	Prediction	Visible light	Resistant starch
Fluoridated	IL-3	Histamine	Diclofan	Emu oil	Risk		Roofos
Fluoride	IL-6	Human placental extract (placentrex) (Kaushal 2001)	Doxepin	Enzyme	Selection		Short-chain fatty acids
Hygienist	Immunologic factors	Hydrocortisone	Fentanyl	Folate	SNPs		Stool softener
Lip balm	Insulin-like growth factor	Ibuprofen	Film	Folic acid			Targin
Mixed medication mouthwashes	Interleukins	Indomethacin	Fluconazole	Folinic acid			Teas

Table 1 (continued)

Basic oral care/good clinical practice	Growth factors and cytokines	Anti-inflammatory agents	Antimicrobials, coating agents, anesthetics, analgesics	Natural therapies and miscellaneous	Pathogenesis	Lasers	GI
Moisturizer	Intestinal trefoil factor	Infliximab	Gelclair	Glutamine			
Mouthcare	Keratinocyte growth factor	Irsogladine	Hydromorphone	Glycerin			
Mouthcare protocol/regimen	Lactoferrin	Lactermin	Ib-367	Gum			
Mouthwash	Macrophage colony-stimulating factor	Lactoferrin	Isegran	Herbal			
Multidisciplinary	Milk-derived growth factor extract	Mesalazine	Kefir	Homeopathic			
Non-medicated rinse	Milk-derived protein	Misoprostol	Kopectate	Honey			
Nurse	Palifermin	N-Acetyl cysteine	Ketamine	Hydrolytic enzyme			
Nursing	Platelet-derived growth factor	Non-steroidal anti-inflammatory agents	Lidocaine	Intestinal trefoil factor			
Nursing oral care/oral hygiene/mouthcare protocol/regimen	PV701	NSAIDS	Local anesthetic	Jelly			
Oral bandage	Repifermin	Orgotein	“Magic” or “miracle” rinses	Lactoferrin			
Oral care	Somatomedins	Prednisone	Magnesium hydroxide	L-glutamine			
Oral care protocol/regimen	Teduglutide	Prostaglandin	Methadone	Licorice			
Oral decontamination	TGF- β	RK-02-02	Midline mucosa sparing blocks	Mf 5232 (mucotrol), a concentrated oral polyherbal gel wafer formulation			
Oral hygiene	Thrombopoietin	Salicylic acid	Morphine	Milk			
Oral hygiene protocol/regimen	TNF	Steroid	Mouth rinse or mouthwash	Milk growth factors			
Oral rinse	TNF alpha	Thalidomide	Mucoadhesive	Milk-derived protein extract			
Oral/mouth/mucositis assessment	Transforming growth factors	TNF antibody	MuGuard	Multivitamin			
Oral/mouth/mucositis examination	Vascular endothelial growth factor	TNF inhibitor	Neuropathic	Natural			
Patient education	Velafermin	Tumor necrosis factor/TNF	Nociceptive	Payayor			
Plaque	Whey protein		Patient controlled	Pentoxifylline			
Provider education			Polymyxin	Pilocarpine			

Table 1 (continued)

Basic oral care/good clinical practice	Growth factors and cytokines	Anti-inflammatory agents	Antimicrobials, coating agents, anesthetics, analgesics	Natural therapies and miscellaneous	Pathogenesis	Lasers	GI
Saline			Polyvinylpyrrolidone	Polaprezinc			
Scaling			Povidone-iodine	Propantheline anticholinergic			
Sodium bicarbonate			Protegrin	Propolis			
Staff education			Sucralfate	PV-701			
Superoxide dismutase (SOD)			Systemic medications	Radiation: morning versus evening			
Toothbrush			Tetracaine	Reduction of mix in anti-gvhd prophylactic protocol before hst			
Toothbrushing			Tetracycline	Retinoid			
Toothpaste			Tobramycin	Rose			
Water			Topical	Shenqi-fanghou			
			Ulcerase	Sodium hyaluronate			
			Xylocaine	Suction cups			
			Zilactin	Tetrachlorodecaoxide (tcd)			
			Zinc*	(oxoferin)			
				Traumeel			
				Tretinoin			
				Vitamin			
				Wax			
				Xanthan			
				Yangyin-humo decoction			
				Yeast			

Zinc was moved to the natural and misc. section during the paper review process
Cryotherapy keywords are listed in Table 2 due to the small number of keywords

Table 2 Modules used for the search algorithm

	Statement	Search strategy
Module	Anatomical—all sections on oral mucositis	(oral OR oropharyngeal OR oropharynx OR mouth)
	Anatomical—GI section	(GI OR Gastrointestinal OR (mucous membrane*) OR mucosa*)
	Anatomical—pathogenesis	(oral OR oropharyngeal OR oropharynx OR mouth OR GI OR Gastrointestinal OR (mucous membrane*) OR mucosa*)
	Cancer	cancer[<i>sb</i>]
	Mucositis—all sections on oral mucositis	(mucositis OR stomatitis OR oral mucous membrane OR oral mucosa* OR oral ulcer* OR oropharyngitis)
	Mucositis—GI section	(mucositis OR (mucosal injury) OR colitis OR enteritis OR ileitis OR enterocolitis OR esophagitis OR gastritis OR proctitis)
	Filter 1	((“2011/01/01”[PDat]: “2016/06/30”[PDat]) AND English[<i>lang</i>])
	Filter 2	NOT (case report OR Review[<i>publication type</i>])
	Filter 3	NOT (“Animals”[<i>Mesh</i>] NOT (“Animals”[<i>Mesh</i>] AND “Humans”[<i>Mesh</i>]))
	Section: antimicrobials, coating agents, anesthetics, and analgesics	((Magic rinse) OR (Miracle rinse) OR Acyclovir OR Adhesive OR Alfentanil OR (aluminum hydroxide) OR (amphotericin B) OR analgesia OR Analgesic OR Antiacid OR antibiotic OR (anti-infective) OR (aqua oral) OR benzocaine OR buprenorphine OR clarithromycin OR clonidine OR coating agent OR Diclosan OR Doxepin OR Fentanyl OR Film OR fluconazole OR Gelclair OR Hydromorphone OR (IB-367) OR Iseganan OR Kefir OR Kaopectate OR Ketamine OR lidocaine OR (Local anesthetic) OR (Magnesium hydroxide) OR Methadone OR Morphine OR Mouthrinse OR Mouthwash OR mucoadhesive OR MuGard OR (Patient controlled) OR polymyxin OR Polyvinylpyrrolidone OR (povidone-iodine) OR Protegrin OR sucalfate OR Tetracaine OR tetracycline OR tobramycin OR Topical OR (Ulcer ease) OR xylocaine OR zilactin OR Zinc)
	Section: anti-inflammatories	(Anti-inflammatory Agents OR Aminosalicilic acid OR Amlexanox OR Anti-inflammatory OR antiinflammatory OR Anti-TNF OR Anti-tumor necrosis factor OR Aspirin OR Benadryl OR Benzydamine OR Betamethasone OR Celecoxib OR Corticosteroid OR Dexamethasone OR Diphenhydramine OR Ethylol OR Flurbiprofen OR Histamine OR Human placental extract OR Hydrocortisone OR Ibuprofen OR Indomethacin OR Infliximab OR Irsogladine OR Lactermin OR Lactoferrin OR Mesalazine OR Misoprostol OR N-Acetyl cysteine OR Non-steroidal anti-inflammatory OR NSAIDS OR Orgotein OR placentex OR Prednisone OR Prostaglandin OR RK-02-02 OR Salicylic acid OR Steroid OR Thalidomide OR TNF OR TNF antibody OR anti-TNF therapy OR TNF inhibitor OR Tumor necrosis factor)
	Section: basic oral care	((Basic oral care) OR (Oral Care) OR (Artificial Saliva) OR Assessment OR (Baking soda) OR (Bland Rinse) OR Brush* OR (Calcium Phosphate) OR Calculus OR Caphsol OR (Caregiver education) OR Chlorhexidine OR Dental OR (dental care) OR (Dental cleaning) OR (Dental Floss) OR Dentist OR Education OR Examination OR (Family education) OR Floss* OR Fluorid* OR Hygiene OR Hygienist OR (Lip balm) OR (Mixed Medication Mouthwash*) OR Moisturizer OR Mouthcare OR (Mouth Care) OR Mouthwash OR Multidisciplinary OR (Non-medicated rinse) OR Nurs* OR (Oral bandag*) OR (Oral Care) OR (Oral Care Regimen) OR (Oral decontamination) OR (Oral Hygiene) OR (Patient education) OR Plaque OR (Provider education) OR Rinse OR Saline OR Scaling OR (Sodium bicarbonate) OR (Staff education) OR (Superoxide dismutase) OR Toothbrush OR Toothbrush* OR Toothpast* OR Water)
	Section: cryotherapy	(Cryotherapy OR Cryotherap* OR Cold OR (Cold Therap*) OR (Cold Temperature*) OR (Cold Water*) OR Freeze OR Freezing OR Froze OR Frozen OR Ice OR (ice water*) OR Icy)
	Section: growth factors and cytokines	((ATL 104) OR (Colony-Stimulating Factors) OR (Cytokines) OR (Epidermal Growth Factor) OR (Fibroblast Growth Factors) OR (Glucagon-like Peptide 2) OR (Granulocyte Colony-Stimulating Factor)

Table 2 (continued)

	Statement	Search strategy
		OR (Granulocyte-Macrophage Colony-Stimulating Factor) OR (IL-11) OR (IL-3) OR (Insulin-like Growth Factor) OR (Interleukins) OR (Keratinocyte Growth Factor) OR (Lactoferrin) OR (Macrophage Colony-Stimulating Factor) OR (Palifermin) OR (Repifermin) OR (TGF- β) OR (TNF) OR (TNF Alpha) OR (Transforming Growth Factors) OR (Velafermin) OR (Whey Protein) OR (Erythropoietin) OR (Thrombopoietin) OR (Carcinoembryonic Antigen Cell Adhesion Molecule 1) OR (Ghrelin) OR (Glutathione) OR (Hepatocyte Growth Factor) OR (Intestinal Trefoil Factor) OR (Milk-derived Growth Factor Extract) OR (Milk-derived Protein) OR (Platelet-derived Growth Factor) OR (PV701) OR (Somatomedins) OR (Teduglutide) OR (Vascular Endothelial Growth Factor) OR (Amino Acids) OR (Immunologic Factors) OR (ALD518 IL-6))
	Section: lasers	(Lasers OR Laser OR LLLT OR (Low level laser therapy) OR (Light therapy) OR Phototherapy OR (Low-level laser) OR LED OR (Light-emitting diode) OR Diode OR (Visible light) OR (He-Ne) OR InGaAlP OR GaAlAs OR InGaAs OR CO2 OR (Infra-red) OR Photobiomodulation))
	Section: natural and miscellaneous remedies	(natural remedies OR natural remedy OR natural therapeutic OR natural therapies OR natural therapy OR allopurinol OR aloe OR aloe vera OR alternative OR azelastine hydrochloride OR azulene OR bee OR beta carotene OR bethanechol OR calcium phosphate OR capsaicin OR fgf 20 OR cg53135 OR chamomile OR chewing gum OR chinese medicine OR chitosan OR clonidine OR colchicine OR complementary OR curcumin OR doxepin OR dyclonine OR emu oil OR enzyme OR folate OR folic acid OR folinic acid OR gabapentin OR glutamine OR glycerin OR gum OR herbal OR homeopathic OR honey OR human placental extract OR placentex OR humidification OR hydrolytic enzyme OR hyperbaric oxygen OR intestinal trefoil factor OR jelly OR lactobacillus OR lactoferrin OR l glutamine OR licorice OR aluminum hydroxide OR magnesium hydroxide OR manuka oil OR anuka OR milk OR mucotrol OR multivitamin OR natural OR payayor OR pentoxifylline OR pilocarpine OR polaprezinc OR propantheline OR propolis OR pv 701 OR radiation OR retinoid OR rhodiola algida OR rose OR shenqi OR collagen OR amino acid OR amino acids OR sodium hyaluronate OR suction cups OR tetrachlorodecaoxide OR tcdo OR oxoferin OR traumeel OR tretinoin OR vitamin OR vitamin a OR vitamin e OR wax OR wobe mugos OR wobe mugos e OR xathan OR yeast)
	Section: gastrotintestinal (GI)	((Glucagon-like peptide-1) OR (Glucagon-like peptide-2) OR (Short chain fatty acids) OR (microbiome sequencing) OR Inulin OR Prebiotics OR Probiotics OR (Resistant starch) OR (Dietary constituents) OR (Dietary supplements) OR Ginger OR Peppermint OR Teas OR Rooibos OR Herbs OR Exercise OR (Stool softener) OR Laxative OR (Oxycodone-naloxone) OR Targin OR (AMP-18) OR (Short chain fatty acids) OR diarrhea)
	Pathogenesis—oral	(Prediction OR Microbiota OR Personalised OR Precision OR Pharmacogenomics OR Prediction OR Selection OR Immunotherapy OR mTOR OR Gut-brain axis OR Epigenetics OR miRNA OR Microbiome OR Sequencing OR Risk OR Microarray OR (Bayesian network) OR SNPs OR Pharmacogenetics OR Model OR Neuroimmune)
	Pathogenesis—GI	(Microbiota OR Immunotherapy OR mTOR OR Gut-brain axis OR Epigenetics OR miRNA OR Microbiome OR Sequencing OR Microarray OR Model OR Neuroimmune)
Complete section statement included a combination of the following modules	Antimicrobials, coating agents, anesthetics, and analgesics	<ul style="list-style-type: none"> • Anatomical—all sections on oral mucositis • Cancer • Mucositis—all sections on oral mucositis • Filter 1 + 2 + 3 • Section: antimicrobials, coating agents, anesthetics, and analgesics
	Anti-inflammatories	<ul style="list-style-type: none"> • Anatomical—all sections on oral mucositis

Table 2 (continued)

Statement	Search strategy
Basic oral care	<ul style="list-style-type: none"> • Cancer • Mucositis—all sections on oral mucositis • Filter 1 + 2 + 3 • Section: anti-inflammatories
Cryotherapy	<ul style="list-style-type: none"> • Anatomical—all sections on oral mucositis • Cancer • Mucositis—all sections on oral mucositis • Filter 1 + 2 + 3 • Section: basic oral care
Growth factors and cytokines	<ul style="list-style-type: none"> • Anatomical—all sections on oral mucositis • Cancer • Mucositis—all sections on oral mucositis • Filter 1 + 2 + 3 • Section: growth factors and cytokines
Lasers	<ul style="list-style-type: none"> • Anatomical—all sections on oral mucositis • Cancer • Mucositis—all sections on oral mucositis • Filter 1 + 2 + 3 • Section: lasers
Natural and miscellaneous remedies	<ul style="list-style-type: none"> • Anatomical—all sections on oral mucositis • Cancer • Mucositis—all sections on oral mucositis • Filter 1 + 2 + 3 • Section: natural and miscellaneous remedies
Gastrointestinal (GI)	<ul style="list-style-type: none"> • Anatomical—GI section • Cancer • Mucositis—GI section • Filter 1 + 2 + 3 • Section: gastrointestinal (GI)
Pathogenesis	<ul style="list-style-type: none"> • Anatomical—all sections on oral mucositis • Cancer • Mucositis—all sections on oral mucositis • Filter 1 + 2 + 3 • Section: pathogenesis—GI • Section: pathogenesis—oral

Following this, the librarians translated the PubMed search strategy for all sections into searches appropriate for Web of Science (WoS). The Natural and Miscellaneous was the section producing the largest number of papers from the PubMed and WoS searches. We therefore piloted the search strategy for EMBASE with this section. No additional relevant papers were identified in the EMBASE search for Natural and Miscellaneous Remedies section. Therefore, it was decided that the EMBASE search would not be conducted for this project.

See Table 2 for the full PubMed strategy. Tables 3 and 4 contain the final search statements used in PubMed and WoS, respectively (available online).

The medical librarians input the search results from each section into EndNote libraries, with separate folders for results from PubMed, Web of Science, and identified duplicate articles. EndNote libraries were shared via email with appropriate section heads, along with spreadsheets of the search strategies.

Period of the review

The previous update of the MASCC/ISOO Clinical Practice Guidelines for Mucositis reviewed all the

Table 3 Complete section statement PubMed

Section	PubMed statement
Antimicrobials, coating agents, anesthetics, and analgesics	(mucositis OR stomatitis OR oral mucous membrane OR oral mucosa* OR oral ulcer* OR oropharyngitis) AND cancer[sb] AND (oral OR oropharyngeal OR oropharynx OR mouth) AND ((Magic rinse) OR (Miracle rinse) OR Acyclovir OR Adhesive OR Alfentanil OR (aluminum hydroxide) OR (amphotericin B) OR analgesia OR Analgesic OR Antiacid OR antibiotic OR (anti-infective) OR (aqua oral) OR benzocaine OR buprenorphine OR clarithromycin OR clonidine OR coating agent OR Diclosan OR Doxepin OR Fentanyl OR Film OR fluconazole OR Gelclair OR Hydromorphone OR (IB-367) OR Iseganan OR Kefir OR Kaopectate OR Ketamine OR lidocaine OR (Local anesthetic) OR (Magnesium hydroxide) OR Methadone OR Morphine OR Mouthrinse OR Mouthwash OR mucoadhesive OR MuGard OR (Patient controlled) OR polymyxin OR Polyvinylpyrrolidone OR (povidone-iodine) OR Protegrin OR sucalfate OR Tetracaine OR tetracycline OR tobramycin OR Topical OR (Ulcer ease) OR xylocaine OR zilactin OR Zinc) NOT (case report OR Review[publication type]) NOT (“Animals”[Mesh] NOT (“Animals”[Mesh] AND “Humans”[Mesh])) AND (“2011/01/01”[PDat]: “2016/06/30”[PDat]) AND English[lang])
Anti-inflammatories	(mucositis OR stomatitis OR oral mucous membrane OR oral mucosa* OR oral ulcer* OR oropharyngitis) AND cancer[sb] AND (oral OR oropharyngeal OR oropharynx OR mouth) AND (Anti-inflammatory Agents OR Aminosalicylic acid OR Amlexanox OR Anti-inflammatory OR antiinflammatory OR Anti-TNF OR Anti-tumor necrosis factor OR Aspirin OR Benadryl OR Benzydamine OR Betamethasone OR Celecoxib OR Corticosteroid OR Dexamethasone OR Diphenhydramine OR Ethylol OR Flurbiprofen OR Histamine OR Human placental extract OR Hydrocortisone OR Ibuprofen OR Indomethacin OR Infliximab OR Irsogladine OR Lactermin OR Lactoferrin OR Mesalazine OR Misoprostol OR N-Acetyl cysteine OR Non-steroidal anti-inflammatory OR NSAIDS OR Orgotein OR placentex OR Prednisone OR Prostaglandin OR RK-02-02 OR Salicylic acid OR Steroid OR Thalidomide OR TNF OR TNF antibody OR anti-TNF therapy OR TNF inhibitor OR Tumor necrosis factor) NOT (case report OR Review[publication type]) NOT (“Animals”[Mesh] NOT (“Animals”[Mesh] AND “Humans”[Mesh])) AND (“2011/01/01”[PDat]: “2016/06/30”[PDat]) AND English[lang])
Basic oral care	(mucositis OR stomatitis OR oral mucous membrane OR oral mucosa* OR oral ulcer* OR oropharyngitis) AND cancer[sb] AND (oral OR oropharyngeal OR oropharynx OR mouth) AND ((Basic oral care) OR (Oral Care) OR (Artificial Saliva) OR Assessment OR (Baking soda) OR (Bland Rinse) OR Brush* OR (Calcium Phosphate) OR Calculus OR Caphosol OR (Caregiver education) OR Chlorhexidine OR Dental OR (dental care) OR (Dental cleaning) OR (Dental Floss) OR Dentist OR Education OR Examination OR (Family education) OR Floss* OR Fluorid* OR Hygiene OR Hygienist OR (Lip balm) OR (Mixed Medication Mouthwash*) OR Moisturizer OR Mouthcare OR (Mouth Care) OR Mouthwash OR Multidisciplinary OR (Non-medicated rinse) OR Nurs* OR (Oral bandag*) OR (Oral Care) OR (Oral Care Regimen) OR (Oral decontamination) OR (Oral Hygiene) OR (Patient education) OR Plaque OR (Provider education) OR Rinse OR Saline OR Scaling OR (Sodium bicarbonate) OR (Staff education) OR (Superoxide dismutase) OR Toothbrush OR Toothbrush* OR Toothpast* OR Water) NOT (case report OR Review[publication type]) NOT (“Animals”[Mesh] NOT (“Animals”[Mesh] AND “Humans”[Mesh])) AND (“2011/01/01”[PDat]: “2016/06/30”[PDat]) AND English[lang])
Cryotherapy	(mucositis OR stomatitis OR oral mucous membrane OR oral mucosa* OR oral ulcer* OR oropharyngitis) AND cancer[sb] AND (oral OR oropharyngeal OR oropharynx OR mouth) AND (Cryotherapy OR Cryotherap* OR Cold OR (Cold Therap*) OR (Cold Temperature*) OR (Cold Water*) OR Freeze OR Freezing OR Froze OR Frozen OR Ice OR (ice water*) OR Icy) NOT (case report OR Review[publication type]) NOT (“Animals”[Mesh] NOT (“Animals”[Mesh] AND “Humans”[Mesh])) AND (“2011/01/01”[PDat]: “2016/06/30”[PDat]) AND English[lang])
Growth factors and cytokines	(mucositis OR stomatitis OR oral mucous membrane OR oral mucosa* OR oral ulcer* OR oropharyngitis) AND cancer[sb] AND (oral OR oropharyngeal OR oropharynx OR mouth) AND ((ATL 104) OR (Colony-Stimulating Factors) OR (Cytokines) OR (Epidermal Growth Factor) OR (Fibroblast Growth Factors) OR (Glucagon-like Peptide 2) OR (Granulocyte Colony-Stimulating Factor) OR (Granulocyte-Macrophage Colony-Stimulating Factor) OR (IL-11) OR (IL-3) OR (Insulin-like Growth Factor) OR (Interleukins) OR (Keratinocyte Growth Factor) OR (Lactoferrin) OR (Macrophage Colony-Stimulating Factor) OR (Palifermin) OR (Repifermin) OR (TGF-b) OR (TNF) OR (TNF Alpha) OR (Transforming Growth Factors) OR (Velafermin) OR (Whey Protein) OR (Erythropoietin) OR (Thrombopoietin) OR (Carcinoembryonic Antigen Cell Adhesion Molecule 1) OR (Ghrelin) OR (Glutathione) OR (Hepatocyte Growth Factor) OR (Intestinal Trefoil Factor) OR (Milk-derived Growth Factor Extract) OR (Milk-derived Protein) OR (Platelet-derived Growth Factor) OR (PV701) OR (Somatomedins) OR (Teduglutide) OR (Vascular Endothelial Growth Factor) OR (Amino Acids) OR (Immunologic Factors) OR (ALD518 IL-6)) NOT (case report OR Review[publication type]) NOT (“Animals”[Mesh] NOT (“Animals”[Mesh] AND “Humans”[Mesh])) AND (“2011/01/01”[PDat]: “2016/06/30”[PDat]) AND English[lang]) Sort by: PublicationDate

Table 3 (continued)

Section	PubMed statement
Lasers	(mucositis OR stomatitis OR oral mucous membrane OR oral mucosa* OR oral ulcer* OR oropharyngitis) AND cancer[sb] AND (oral OR oropharyngeal OR oropharynx OR mouth) AND (Lasers OR Laser OR LLLT OR (Low level laser therapy) OR (Light therapy) OR Phototherapy OR (Low-level laser) OR LED OR (Light-emitting diode) OR Diode OR (Visible light) OR (He-Ne) OR InGaAlP OR GaAlAs OR InGaAs OR CO2 OR (Infra-red) OR Photobiomodulation) NOT (case report OR Review[publication type]) NOT (“Animals”[Mesh] NOT (“Animals”[Mesh] AND “Humans”[Mesh])) AND (“2011/01/01”[PDat]: “2016/06/30”[PDat]) AND English[lang]) Sort by: PublicationDate
Natural and miscellaneous remedies	(mucositis OR stomatitis OR oral mucous membrane OR oral mucosa* OR oral ulcer* OR oropharyngitis) AND cancer[sb] AND (oral OR oropharyngeal OR oropharynx OR mouth) AND (natural remedies OR natural remedy OR natural therapeutic OR natural therapies OR natural therapy OR allopurinol OR aloe OR aloe vera OR alternative OR azelastine hydrochloride OR azulene OR bee OR beta carotene OR bethanechol OR calcium phosphate OR capsaicin OR fgf 20 OR eg53135 OR chamomile OR chewing gum OR chinese medicine OR chitosan OR clonidine OR colchicine OR complementary OR curcumin OR doxepin OR dyclonine OR emu oil OR enzyme OR folate OR folic acid OR folinic acid OR gabapentin OR glutamine OR glycerin OR gum OR herbal OR homeopathic OR honey OR human placental extract OR placentex OR humidification OR hydrolytic enzyme OR hyperbaric oxygen OR intestinal trefoil factor OR jelly OR lactobacillus OR lactoferrin OR l glutamine OR licorice OR aluminum hydroxide OR magnesium hydroxide OR manuka oil OR anuka OR milk OR mucotrol OR multivitamin OR natural OR payayor OR pentoxifylline OR pilocarpine OR polaprezinc OR propantheline OR propolis OR pv 701 OR radiation OR retinoid OR rhodiola algida OR rose OR shenqi OR collagen OR amino acid OR amino acids OR sodium hyaluronate OR suction cups OR tetrachlorodecaoxide OR tcdo OR oxoferin OR traumeel OR tretinoin OR vitamin OR vitamin a OR vitamin e OR wax OR wobe mugos OR wobe mugos e OR xathan OR yeast) NOT (case report OR Review[publication type]) NOT (“Animals”[Mesh] NOT (“Animals”[Mesh] AND “Humans”[Mesh])) Filters: Publication date from 2011/01/01 to 2016/06/30; English Sort by: PublicationDate
Gastrointestinal (GI)	(mucositis OR (mucosal injury) OR colitis OR enteritis OR ileitis OR enterocolitis OR esophagitis OR gastritis OR proctitis) AND cancer[sb] AND (GI OR Gastrointestinal OR (mucous membrane*) OR mucosa*) AND ((Glucagon-like peptide-1) OR (Glucagon-like peptide-2) OR (Short chain fatty acids) OR (microbiome sequencing) OR Inulin OR Prebiotics OR Probiotics OR (Resistant starch) OR (Dietary constituents) OR (Dietary supplements) OR Ginger OR Peppermint OR Teas OR Rooibos OR Herbs OR Exercise OR (Stool softener) OR Laxative OR (Oxycodone-naloxone) OR Targin OR (AMP-18) OR (Short chain fatty acids) OR diarrhea) NOT (case report OR Review[publication type]) NOT (“Animals”[Mesh] NOT (“Animals”[Mesh] AND “Humans”[Mesh])) AND (“2011/01/01”[PDat]: “2016/06/30”[PDat]) AND English[lang]) Sort by: PublicationDate
Pathogenesis—oral	(mucositis OR stomatitis OR oral mucous membrane OR oral mucosa* OR oral ulcer*) AND cancer[sb] AND (oral OR oropharyngeal OR oropharynx OR mouth) AND (Prediction OR Microbiota OR Personalised OR Precision OR Pharmacogenomics OR Prediction OR Selection OR Immunotherapy OR mTOR OR Gut-brain axis OR Epigenetics OR miRNA OR Microbiome OR Sequencing OR Risk OR Microarray OR (Bayesian network) OR SNPs OR Pharmacogenetics OR Model OR Neuroimmune) NOT (case report OR Review [Publication Type]) AND (“2011/01/01”[PDat]: “2016/06/30”[PDat]) AND English[lang]) Sort by: PublicationDate
Pathogenesis—GI	(mucositis OR (mucosal injury) OR colitis OR enteritis OR ileitis OR enterocolitis OR esophagitis OR gastritis OR proctitis) AND cancer[sb] AND (GI OR Gastrointestinal OR (mucous membrane*) OR mucosa*) AND (Prediction OR Microbiota OR Personalised OR Precision OR Pharmacogenomics OR Prediction OR Selection OR Immunotherapy OR mTOR OR Gut-brain axis OR Epigenetics OR miRNA OR Microbiome OR Sequencing OR Risk OR Microarray OR (Bayesian network) OR SNPs OR Pharmacogenetics OR Model OR Neuroimmune) NOT (case report OR Review [Publication Type]) AND (“2011/01/01”[PDat]: “2016/06/30”[PDat]) AND English[lang]) Sort by: PublicationDate

literature available until the end of 2010 [4]. For this review, a significant number of papers had been identified from the searches for the timeframe from January 2011 until June 2016. Because the principles of manuscript reviewing and evidence analysis were similar to the previous guidelines update, this

systematic review could focus solely on the data published since 2010 and merge this into the evidence from the previous reviews. Papers published after the timeframe of the review were addressed in the Discussion to indicate future trends and consistency with the current guidelines.

Table 4 Complete section statement Web of Science

Section	Web of Science statement
Antimicrobials, coating agents, anesthetics, and analgesics	<p>TS=((Mucosit* OR Stomatit* OR Oromucosit* OR Oropharyngit* OR Mucosa* OR Ulcer* OR (muco\$s* NEAR/2 membran*) OR (mucosa* NEAR/2 barrier)) AND ((bone marrow NEAR/2 transplant*) OR (condition* NEAR/2 regimen*) OR (Hemato NEAR/2 Oncolog*) OR (hematopoietic NEAR/2 stem cell* NEAR/2 transplant*) OR antineoplastic* OR biochemotherap* OR Cancer* OR Carcin* OR carcinogen* OR chemotherap* OR cytotoxic* OR Hematolo* OR Hematooncological OR Hemato-Oncological OR leuk\$emia* OR lymphoma* OR Malignan* OR Neoplasm* OR Oncolog* OR radiotherap* OR tumo\$r*) AND (Mouth OR Oral* OR buccal* OR Oropharyn* OR (Oris NEAR/2 Cavitas) OR (Vestibule NEAR/2 Oris)) AND ((Magic rinse) OR (Miracle rinse) OR Acyclovir OR Adhesive OR Alfentanil OR (aluminum hydroxide) OR (amphotericin B) OR analgesia OR Analgesic OR Antacid OR antibiotic OR (anti-infective) OR (aqua oral) OR benzocaine OR buprenorphine OR clarithromycin OR clonidine OR coating agent OR Diclosan OR Doxepin OR Fentanyl OR Film OR fluconazole OR Gelclair OR Hydromorphone OR (IB-367) OR Isegaran OR Kefir OR Kaopectate OR Ketamine OR lidocaine OR (Local anesthetic) OR (Magnesium hydroxide) OR Methadone OR Morphine OR Mouthrinse OR Mouthwash OR mucoadhesive OR MuGard OR (Patient controlled) OR polymyxin OR Polyvinylpyrrolidone OR (povidone-iodine) OR Protegrin OR sucralfate OR Tetracaine OR tetracycline OR tobramycin OR Topical OR (Ulcer ease) OR xylocaine OR zilactin OR Zinc)) NOT TI=(rat* OR mouse OR mice OR rabbit* OR dog* OR murine OR “animal model” OR “in vivo” OR “in vitro”) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Letter OR Proceedings Paper) Indexes=SCI-EXPANDED, ESCI Timespan=2011-2016</p>
Anti-inflammatories	<p>TS=((Anti-inflammatory Agents) OR anti-inflammator* OR antiinflammator* OR (Aminosalicylic acid) OR “Aminosalicylic Acid” OR Amlexanox OR Anti-inflammatory OR antiinflammator OR (Anti-TNF) OR AntiTNF OR (Anti-tumor necrosis factor) OR “Anti-tumo\$r necrosis factor” OR “Antitumo\$r necrosis factor” OR Aspirin OR Benadryl OR Benzydamine OR Betamethasone OR Celecoxib OR Corticosteroid OR Dexamethasone OR Diphenhydramine OR Ethylol OR Flurbiprofen OR Histamine OR (Human placental extract) OR (Human NEAR/2 placent* NEAR/2 extract*) OR Hydrocortisone OR Ibuprofen OR Indomethacin OR Infliximab OR Irsogladine OR Lacternin OR Lactoferrin OR Mesalazine OR Misoprostol OR (N-Acetyl cysteine) OR “N-Acetyl cysteine” OR “NAcetyl cysteine” OR (Non-steroidal anti-inflammatory) OR NSAIDS OR NSAID* OR Orgotein OR placentex OR Prednisone OR Prostaglandin OR (RK-02-02) OR “RK-02-02” OR (Salicylic acid) OR “Salicylic acid” OR Steroid OR Thalidomide OR TNF OR (TNF antibody) OR (TNF NEAR/2 (antibod* OR inhibitor*)) OR (anti-TNF therapy) OR (TNF inhibitor) OR (Tumor necrosis factor) OR (Tumo\$r NEAR/2 necrosis NEAR/2 factor*)) AND (TS= (Mouth OR Oral* OR buccal* OR Oropharyn* OR (Oris NEAR/2 Cavitas) OR (Vestibule NEAR/2 Oris))) AND (TS=((bone marrow NEAR/2 transplant*) OR (condition* NEAR/2 regimen*) OR (Hemato NEAR/2 Oncolog*) OR (hematopoietic NEAR/2 stem cell* NEAR/2 transplant*) OR antineoplastic* OR biochemotherap* OR Cancer* OR Carcin* OR carcinogen* OR chemotherap* OR cytotoxic* OR Hematolo* OR Hematooncological OR Hemato-Oncological OR leuk\$emia* OR lymphoma* OR Malignan* OR Neoplasm* OR Oncolog* OR radiotherap* OR tumo\$r*) AND (TS= (Mucosit* OR Stomatit* OR Oromucosit* OR Oropharyngit* OR Mucosa* OR Ulcer* OR (muco\$s* NEAR/2 membran*) OR (mucosa* NEAR/2 barrier))) NOT TI=(rat* OR mouse OR mice OR rabbit* OR dog* OR murine OR “animal model” OR “in vivo” OR “in vitro”) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Letter OR Proceedings Paper) Indexes=SCI-EXPANDED, ESCI Timespan=2011-2016</p>
Basic oral care	<p>TS=((Basic oral care) OR (oral care AND (basic* OR decontaminat* OR hygien* OR regimen*)) OR (Oral Care) OR (Artificial Saliva) OR (artificial NEAR/3 saliva) OR Assessment OR (Baking soda) OR (Bland Rinse) OR Brush* OR (Calcium Phosphate) OR Calculus OR Caphosol OR (Caregiver education) OR ((Caregiv* OR Famil*) AND educat*) OR Chlorhexidine OR Dental OR (dental care) OR (Dental cleaning) OR (Dental Floss) OR (Dental AND (car* OR clean* OR floss*)) OR Dentist OR Education OR Educat* OR Examination OR Exam* OR (Family education) OR (educat* AND (caregiv* OR famil* OR patient* OR provider* OR staff)) OR Floss* OR Fluorid* OR Hygiene OR Hygienist OR Hygien* OR (Lip balm) OR (Mixed Medication Mouthwash*) OR (Mixed Medication AND (mouthwash* OR mouth wash*)) OR Moisturizer OR Moisturiz* OR Mouthcare OR (Mouth Care) OR mouthcare* OR (mouth care*) OR Mouthwash OR Multidisciplinary OR Multidisciplin* OR (Non-medicated rinse) OR ((Non-medicat* OR Nonmedicat*) AND rins*) OR Nurs* OR (Oral bandag*) OR (Oral Care) OR (Oral Care Regimen) OR (Oral decontamination) OR (Oral Hygiene) OR (Patient education) OR Plaque OR (Provider education) OR Rinse rins* OR Saline OR saline OR Scaling OR scaler OR (Sodium bicarbonate) OR (Staff education) OR (Superoxide dismutase) OR Toothbrush OR Toothbrush* OR t*th brush* OR toothbrush* OR Toothpast* OR t*th past* OR toothpast* OR Water) AND TS= (Mouth OR Oral* OR buccal* OR Oropharyn* OR (Oris NEAR/2 Cavitas) OR (Vestibule NEAR/2 Oris)) AND TS=((bone marrow NEAR/2 transplant*) OR (condition* NEAR/2 regimen*) OR (Hemato NEAR/2 Oncolog*) OR (hematopoietic NEAR/2 stem cell* NEAR/2 transplant*) OR antineoplastic* OR biochemotherap* OR Cancer* OR Carcin* OR carcinogen* OR chemotherap* OR cytotoxic* OR</p>

Table 4 (continued)

Section	Web of Science statement
Cryotherapy	<p>Hematolo* OR Hematooncological OR Hemato-Oncological OR leuk\$emia* OR lymphoma* OR Malignan* OR Neoplasm* OR Oncolog* OR radiotherap* OR tumo\$r* AND TS= (Mucosit* OR Stomatit* OR Oromucosit* OR Oropharyngit* OR Mucosa* OR Ulcer* OR (muco\$s\$ NEAR/2 membran*) OR (mucosa* NEAR/2 barrier)) NOT TI=(rat* OR mouse OR mice OR rabbit* OR dog* OR murine OR “animal model” OR “in vivo” OR “in vitro”) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Letter OR Proceedings Paper) Indexes=SCI-EXPANDED, ESCI Timespan=2011-2016</p> <p>TS=((Mucosit* OR Stomatit* OR Oromucosit* OR Oropharyngit* OR Mucosa* OR Ulcer* OR (muco\$s\$ NEAR/2 membran*) OR (mucosa* NEAR/2 barrier)) AND ((bone marrow NEAR/2 transplant*) OR (condition* NEAR/2 regimen*) OR (Hemato NEAR/2 Oncolog*) OR (hematopoietic NEAR/2 stem cell* NEAR/2 transplant*) OR antineoplastic* OR biochemotherap* OR Cancer* OR Carcin* OR carcinogen* OR chemotherap* OR cytotoxic* OR Hematolo* OR Hematooncological OR Hemato-Oncological OR leuk\$emia* OR lymphoma* OR Malignan* OR Neoplasm* OR Oncolog* OR radiotherap* OR tumo\$r*) AND (Mouth OR Oral* OR buccal* OR Oropharyn* OR (Oris NEAR/2 Cavitas) OR (Vestibule NEAR/2 Oris)) AND (Cryotherapy OR Cryotherap* OR Cold OR (Cold Therap*) OR (Cold Temperature*) OR (Cold Water*) OR Freeze OR Freezing OR Froze OR Frozen OR Ice OR (ice water*) OR Icy)) NOT TI=(rat* OR mouse OR mice OR rabbit* OR dog* OR murine OR “animal model” OR “in vivo” OR “in vitro”) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Letter OR Proceedings Paper) Indexes=SCI-EXPANDED, ESCI Timespan=2011-2016</p>
Growth factors and cytokines	<p>TS= (Mucosit* OR Stomatit* OR Oromucosit* OR Oropharyngit* OR Mucosa* OR Ulcer* OR (muco\$s\$ NEAR/2 membran*) OR (mucosa* NEAR/2 barrier)) AND TS=((bone marrow NEAR/2 transplant*) OR (condition* NEAR/2 regimen*) OR (Hemato NEAR/2 Oncolog*) OR (hematopoietic NEAR/2 stem cell* NEAR/2 transplant*) OR antineoplastic* OR biochemotherap* OR Cancer* OR Carcin* OR carcinogen* OR chemotherap* OR cytotoxic* OR Hematolo* OR Hematooncological OR Hemato-Oncological OR leuk\$emia* OR lymphoma* OR Malignan* OR Neoplasm* OR Oncolog* OR radiotherap* OR tumo\$r*) AND TS= (Mouth OR Oral* OR buccal* OR Oropharyn* OR (Oris NEAR/2 Cavitas) OR (Vestibule NEAR/2 Oris)) AND TS=((ATL 104) OR “ATL 104” OR (Colony-Stimulating Factors) OR Cytokines OR Cytokine* OR (Epidermal Growth Factor) OR (Fibroblast Growth Factors) OR (Glucagon-like Peptide 2) OR “Glucagon-like Peptide-2” OR (Granulocyte Colony-Stimulating Factor) OR (Granulocyte-Macrophage Colony-Stimulating Factor) OR ((Granulocyte* OR Macrophage* OR “Granulocyte-Macrophage”) NEAR/2 “Colony-Stimulating Factor”) OR (IL-11) OR “IL-11” OR (IL-3) OR “IL-3” OR (Insulin-like Growth Factor) OR Interleukins OR Interleukin* OR (Keratinocyte Growth Factor) OR Lactoferrin OR Lactoferrin* OR (Macrophage Colony-Stimulating Factor) OR “Colony-Stimulating Factor”) OR Palifermin OR Palifermin* OR Repifermin OR Repifermin* OR (TGF-b) OR “TGF-b” OR TNF OR (TNF Alpha) OR “TNF Alpha” OR (Transforming Growth Factors) OR Velafermin OR Velafermin* OR (Whey Protein) OR (Whey NEAR/2 Protein*) OR Erythropoietin OR Erythropoietin* OR Thrombopoietin OR Thrombopoietin* OR (Carcinoembryonic Antigen Cell Adhesion Molecule 1) OR “Carcinoembryonic Antigen Cell Adhesion Molecule-1” OR Ghrelin OR Ghrelin* OR Glutathione OR Glutathione* OR (Hepatocyte Growth Factor) OR (Intestinal Trefoil Factor) OR “Intestinal Trefoil Factor”) OR (Milk-derived Growth Factor Extract) OR (Milk-derived Protein) OR “Milk-derived Protein”) OR “Milk-derive”) OR (Platelet-derived Growth Factor) OR PV701 OR Somatomedins OR Somatomedin* OR Teduglutide OR Teduglutide* OR (Vascular Endothelial Growth Factor) OR ((Epidermal* OR Fibroblast* OR “Insulin-like” OR Keratinocyte* OR Transform* OR Hepatocyte* OR “Platelet-derive”) OR “Vascular Endothelial”) NEAR/2 “Growth Factor”) OR (Amino Acids) OR “Amino Acid”) OR (Immunologic Factors) OR “Immunologic Factor”) OR (ALD518 IL-6) OR “ALD518” OR “IL-6”) NOT (TI=(rat* OR mouse OR mice OR rabbit* OR dog* OR murine OR “animal model” OR in vivo OR in vitro) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Letter OR Proceedings Paper) Indexes=SCI-EXPANDED, ESCI Timespan=2011-2016</p>
Lasers	<p>TS=((Mucosit* OR Stomatit* OR Oromucosit* OR Oropharyngit* OR Mucosa* OR Ulcer* OR (muco\$s\$ NEAR/2 membran*) OR (mucosa* NEAR/2 barrier)) AND ((bone marrow NEAR/2 transplant*) OR (condition* NEAR/2 regimen*) OR (Hemato NEAR/2 Oncolog*) OR (hematopoietic NEAR/2 stem cell* NEAR/2 transplant*) OR antineoplastic* OR biochemotherap* OR Cancer* OR Carcin* OR carcinogen* OR chemotherap* OR cytotoxic* OR Hematolo* OR Hematooncological OR Hemato-Oncological OR leuk\$emia* OR lymphoma* OR Malignan* OR Neoplasm* OR Oncolog* OR radiotherap* OR tumo\$r*) AND (Mouth OR Oral* OR buccal* OR Oropharyn* OR (Oris NEAR/2 Cavitas) OR (Vestibule NEAR/2 Oris)) AND (Lasers OR Laser OR LLLT OR (Low level laser therapy) OR (Light therapy) OR Phototherapy OR (Low-level laser) OR LED OR (Light-emitting diode) OR Diode OR (Visible light) OR (He-Ne) OR InGaAlP OR GaAlAs OR InGaAs OR CO2 OR (Infra-red) OR Photobiomodulation)) NOT TI=(rat* OR mouse OR mice OR rabbit* OR dog* OR murine OR “animal</p>

Table 4 (continued)

Section	Web of Science statement
Natural and miscellaneous remedies	<p>model” OR “in vivo” OR “in vitro”) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Letter OR Proceedings Paper) Indexes=SCI-EXPANDED, ESCI Timespan=2011-2016</p> <p>TS=((natural remedies) OR (natural remedy) OR (natural NEAR/2 (remedy OR remedies)) OR (natural therapeutic) OR (natural therapies) OR (natural therapy) OR (natural NEAR/2 (therapeut* OR therapy OR therapies)) OR (allopurinol) OR aloe OR (aloe vera) OR alternative OR (azelastine hydrochloride) OR “azelastine hydrochloride” OR azulene OR bee OR (beta carotene) OR “beta carotene” OR bethanechol OR (calcium phosphate) OR “calcium phosphate” OR capsaicin OR (fgf 20) OR “fgf 20” OR cg53135 OR chamomile OR (chewing gum) OR “chew* gum*” OR (chinese medicine) OR “chinese medicine” OR chitosan OR clonidine OR colchicine OR complementary OR curcumin OR doxepin OR dyclonine OR emu oil OR “emu oil*” OR enzyme OR folate OR (folic acid) OR “folic acid*” OR (folinic acid) OR “folinic acid*” OR gabapentin OR glutamine OR glycerin OR gum OR herbal OR homeopathic OR Homeopath* OR honey OR (human placental extract) OR “human placent* extract*” OR placentex OR humidification OR (hydrolytic enzyme) OR “hydrolytic enzyme*” OR (hyperbaric oxygen) OR “hyperbaric oxygen*” OR (intestinal trefoil factor) OR “intestinal trefoil factor*” OR jelly OR lactobacillus OR lactoferrin OR (l glutamine) OR “l glutamine” OR licorice OR Licorice* OR (aluminum hydroxide) OR “aluminum hydroxide” OR (magnesium hydroxide) OR “magnesium hydroxide” OR (manuka oil) OR “manuka oil*” OR anuka OR milk OR mucotrol OR multivitamin OR multivitamin* OR natural OR payayor OR pentoxifylline OR pilocarpine OR polaprezinc OR propantheline OR propolis OR (pv 701) OR “pv 701” OR radiation OR retinoid OR (rhodiola algida) OR “rhodiola algida” OR rose OR rose* OR shenqi OR collagen OR (amino acid) OR (amino acids) OR “amino acid*” OR (sodium hyaluronate) OR “sodium hyaluronate” OR (suction cups) OR “suction cup*” OR tetrachlorodecaoxide OR tcdo OR oxoferin OR traumeel OR tretinoin OR vitamin OR Vitamin* OR vitamin a OR (vitamin e) OR wax OR wax* OR (wobe mugos) OR (wobe mugos e) OR “wobe mugos” OR xathan OR yeast OR Yeast* OR (Hematopoietic NEAR/3 Stem Cell* NEAR/3 Transplant*) OR mouthwash* OR (Transplant* NEAR/4 Condition*) AND TS= (Mouth OR Oral* OR buccal* OR Oropharyn* OR (Oris NEAR/2 Cavitas) OR (Vestibule NEAR/2 Oris)) AND TS=((bone marrow NEAR/2 transplant*) OR (condition* NEAR/2 regimen*) OR (Hemato NEAR/2 Oncolog*) OR (hematopoietic NEAR/2 stem cell* NEAR/2 transplant*) OR antineoplastic* OR biochemotherap* OR Cancer* OR Carcin* OR carcinogen* OR chemotherap* OR cytotoxic* OR Hematolo* OR Hematooncological OR Hemato-Oncological OR leuk\$emia* OR Malignan* OR Neoplasm* OR Oncolog* OR radiotherap* OR tumo\$*) AND TS= (Mucosit* OR Stomatit* OR Oromucosit* OR Oropharyngit* OR Mucosa* OR Ulcer* OR (muco\$s* NEAR/2 membran*) OR (mucosa* NEAR/2 barrier)) NOT TI=(rat* OR mouse OR mice OR rabbit* OR dog* OR murine OR “animal model” OR “in vivo” OR “in vitro”) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Letter OR Proceedings Paper) Indexes=SCI-EXPANDED, ESCI Timespan=2011-2016</p>
Gastrointestinal (GI)	<p>TS=((mucositis OR (mucosal injury) OR colitis OR enteritis OR ileitis OR enterocolitis OR esophagitis OR gastritis OR proctitis) AND ((bone marrow NEAR/2 transplant*) OR (condition* NEAR/2 regimen*) OR (Hemato NEAR/2 Oncolog*) OR (hematopoietic NEAR/2 stem cell* NEAR/2 transplant*) OR antineoplastic* OR biochemotherap* OR Cancer* OR Carcin* OR carcinogen* OR chemotherap* OR cytotoxic* OR Hematolo* OR Hematooncological OR Hemato-Oncological OR leuk\$emia* OR lymphoma* OR Malignan* OR Neoplasm* OR Oncolog* OR radiotherap* OR tumo\$*) AND ((Glucagon-like peptide-1) OR (Glucagon-like peptide-2) OR (Short chain fatty acids) OR (microbiome sequencing) OR Inulin OR Prebiotics OR Probiotics OR (Resistant starch) OR (Dietary constituents) OR (Dietary supplements) OR Ginger OR Peppermint OR Teas OR Rooibos OR Herbs OR Exercise OR (Stool softener) OR Laxative OR (Oxycodone-naloxone) OR Targin OR (AMP-18) OR (Short chain fatty acids) OR diarrhea)) NOT TI=(rat* OR mouse OR mice OR rabbit* OR dog* OR murine OR “animal model” OR “in vivo” OR “in vitro”) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Letter OR Proceedings Paper) Indexes=SCI-EXPANDED, ESCI Timespan=2011-2016</p>
Pathogenesis—oral	<p>TS=((Mucosit* OR Stomatit* OR Oromucosit* OR Oropharyngit* OR Mucosa* OR Ulcer* OR (muco\$s* NEAR/2 membran*) OR (mucosa* NEAR/2 barrier)) AND ((bone marrow NEAR/2 transplant*) OR (condition* NEAR/2 regimen*) OR (Hemato NEAR/2 Oncolog*) OR (hematopoietic NEAR/2 stem cell* NEAR/2 transplant*) OR antineoplastic* OR biochemotherap* OR Cancer* OR Carcin* OR carcinogen* OR chemotherap* OR cytotoxic* OR Hematolo* OR Hematooncological OR Hemato-Oncological OR leuk\$emia* OR lymphoma* OR Malignan* OR Neoplasm* OR Oncolog* OR radiotherap* OR tumo\$*) AND (Mouth OR Oral* OR buccal* OR Oropharyn* OR (Oris NEAR/2 Cavitas) OR (Vestibule NEAR/2 Oris)) AND (Prediction OR Microbiota OR Personalised OR Precision OR Pharmacogenomics OR Prediction OR Selection OR Immunotherapy OR mTOR OR Gut-brain axis OR Epigenetics OR miRNA OR Microbiome OR Sequencing OR Risk OR Microarray OR (Bayesian network) OR SNPs OR Pharmacogenetics OR Model OR Neuroimmune)) AND LANGUAGE: (English)</p>

Table 4 (continued)

Section	Web of Science statement
Pathogenesis—GI	<p>AND DOCUMENT TYPES: (Article OR Letter OR Proceedings Paper) Indexes=SCI-EXPANDED, ESCI Timespan=2011-2016</p> <p>TS=((mucositis OR (mucosal injury) OR colitis OR enteritis OR ileitis OR enterocolitis OR esophagitis OR gastritis OR proctitis) AND ((bone marrow NEAR/2 transplant*) OR (condition* NEAR/2 regimen*) OR (Hemato NEAR/2 Oncolog*) OR (hematopoietic NEAR/2 stem cell* NEAR/2 transplant*) OR antineoplastic* OR biochemotherap* OR Cancer* OR Carcin* OR carcinogen* OR chemotherap* OR cytotoxic* OR Hematolo* OR Hematooncological OR Hemato-Oncological OR leuk\$emia* OR lymphoma* OR Malignan* OR Neoplasm* OR Oncolog* OR radiotherap* OR tumo\$r*) AND (Gastrointestinal OR GI OR (Digestive Tract*) OR (muco\$s\$* NEAR/2 membran*) OR mucosa*) AND (Prediction OR Microbiota OR Personalised OR Precision OR Pharmacogenomics OR Prediction OR Selection OR Immunotherapy OR mTOR OR Gut-brain axis OR Epigenetics OR miRNA OR Microbiome OR Sequencing OR Risk OR Microarray OR (Bayesian network) OR SNPs OR Pharmacogenetics OR Model OR Neuroimmune)) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Letter OR Proceedings Paper) Indexes=SCI-EXPANDED, ESCI Timespan=2011-2016</p>

Considerations related to the effectiveness

The effectiveness of the intervention was presented as per patient population (hematological cancer, solid cancer, head and neck cancer), cancer therapy modality (chemotherapy, radiotherapy, radio-chemotherapy, hematopoietic stem cell transplantation), aim of intervention (prevention or treatment), and as detailed as possible in terms of dose and concentration.

Interventions were reviewed for effectiveness, and this was described in terms of mucositis severity, mucositis duration, pain severity, and pain duration. Information about other reported outcome measures was retrieved and integrated to describe the findings on efficacy.

For the purpose of the review, studies conducted in HSCT patient population were classified as hematological cancer studies. The study population may have included patients with a non-cancer diagnosis. This was done as the effect of the HSCT on the oral mucosa is independent of the diagnosis. Evidence regarding the intensity of the conditioning regimen for HSCT or cancer therapy were assessed as they affected the risk for oral mucositis. In regard to the patient age, the results were stratified as intervention for pediatric and adult population. The wording of the guidelines reflects this stratification.

Criteria for evaluation of scientific evidence

Similar to the guidelines update published in 2014, for the current guidelines update, we applied the Hadorn criteria for evaluation of scientific evidence [8]. The Agency for Health Care Policy and Research originally published these criteria when it sponsored the clinical practice guidelines for the management of patients with heart

failure due to left ventricular systolic dysfunction [8–11]. Briefly, the criteria classify flaws in study design as major and minor flaws. These allow for grading the study and determine the scientific contribution of the study findings. These criteria were modified to meet the requirements of mucositis studies, as described in the previous publication [6]. This process was repeated by two independent reviewers and relayed back separately to the section head. The final decision on any discrepant answers was made by the section head.

Allocating a level of evidence and categories used to classify guidelines

The new evidence was merged with the data from the 2011 systematic review. The most significant contribution from the database of publications prior to 2011 came from randomized controlled trials.

The methods used to determine the level of evidence and classification of guidelines described in a previous paper [6] were adapted from Somerfield paper [11] and followed the MASCC Guidelines Policy [12]. Briefly, evidence was defined according to 5 levels (I–V) and this determined the guideline category as recommendation, suggestion, no guideline possible. If a paper was deemed not well designed as per the Hadorn criteria, it was downgraded to a lower level of evidence.

Positive guidelines were reserved for situations in which strong evidence indicated effectiveness of the intervention in the treatment setting listed. Negative guidelines were reserved for situations in which strong evidence indicated lack of effectiveness in the treatment settings listed. This does not imply that this is a harmful intervention.

For the current update, it was noted that there was an increase in the number of randomized controlled trials (RCTs). However, many of these had a small sample size often with inconclusive results, which limited the applicability of the findings. Therefore, in order to determine a recommendation-type guideline, we looked for multiple RCTs, at least one of them with no major flaws.

Logistics of the review process

A section head and co-head were appointed for each section. Their roles were to coordinate the transfer of papers and review forms between the reviewers and central data storage platform and assist reviewers in review process. In addition, section heads from the previous update were available as consultants to assist and guide with the review.

A call for reviewers was sent to enlist members for the review process. According to the MASCC policy for guidelines development [12], members were asked to disclose any conflicts of interest and the section they would like to participate in. Only members who met the MASCC criteria participated as reviewers. The allocation of members to each section was done based on the reviewer preference and volume of papers to be reviewed. A manual survey on the number of randomized controlled trials (RCTs) for each section was performed prior to the full literature review in order to obtain an estimate about the expected volume of literature in each section. The number of reviewers for each section was proportional to the number of RCTs identified for the section. Reviewers sent their top 3 preferences for section they would like to be included into. To enable uniformity in the review process among different sections, each section head and reviewer was supplied with a set of tools as follows:

1. Section head guide
2. Instructions for section heads/instructions for reviewers
3. Section head form/reviewer form
4. Article flowchart
5. Procedure manual
6. Somerfield and Hadorn papers
7. Section members—email list

Calibration

A demonstration for the use of these tools was created in a PowerPoint format and distributed via email to section heads and co-heads. Online sessions were conducted to review the use of these resources and clarify any questions.

Following this, calibration exercises were carried out using a paper relevant to the topic of this review [13]. Once the

exercise was completed, a key was sent to ensure uniformity among the participants of the review. Subsequently, papers were made available to section heads for distribution to reviewers. Periodic online conferences with section heads were conducted for problem-solving and ensuring consistency in the review process.

To enable the pooling of previous and new data, a criteria sheet was developed to extract relevant data from the previous guideline papers. These data were tabulated in a standard format and provided to all sections to ensure uniformity throughout the review process. The compiled data was presented by each section at a MSG guidelines meeting in Washington June 2017, where a preliminary discussion on allocating the level of evidence and recommendations for guidelines took place.

Platform for online sharing

In the previous update, a single Google drive account was used by all members to access publications and data forms. Since the previous review, numerous changes occurred in the Google drive interphase, which required several modifications in the design of our online sharing plan. For the current guidelines, nine google drive accounts, one for each section was created for bilateral communication of reviewer forms. In addition, a single Google drive with publications from all sections was created for unilateral access to papers. This compartmentalized design was intended to optimize account usage to relevant users. One backup account was also created. Many different Google drive designs were considered. However, due to the security features in Google drive requiring recovery email address and phone numbers, users were locked out of their accounts, and multistep verifications were needed to access back their accounts.

In the final architecture, only section heads were provided with access details to the account, and reviewers were emailed copies of the publications and reviewer forms. These were then sent back to the section heads, who uploaded the completed reviewer form to Google drive. The section-specific drive was then used for communication about the compilation of the two reviewer forms into a single section head form.

The advantages of this system were that data transfer was efficient and ensured minimum errors in transmission of data. Also, as a limited number of persons were accessing each account, any security concerns by Google drive could be managed. Unintentional deleting and duplication of files that were noted when multiple users accessed the same account were avoided.

Conclusion

The methods used were critical for converting a large pool of data into a practical clinical set of guidelines while combining the findings of the recent systematic review with the previous

review. A detailed set of instructions was provided to the group to ensure consistency. The process of updating existing guidelines requires periodic examination of policy and procedures related to guideline production.

Compliance with ethical standards

Conflict of interest Employees of commercial entities were not eligible to serve on this MASCC Guidelines Panel. All authors completed a conflict of interest disclosure form and conflicts are disclosed in the guideline's publications. The authors disclose no conflict of interest (VR, KC, LP, DC). PB has served an advisory role for Galera Therapeutics. SE reports no conflict in regard to mucositis, and consulting to Falk Pharma as the Medical Expert for a clinical trial about oral chronic graft versus host disease. RVL has served as a consultant for Colgate Oral Pharmaceuticals, Galera Therapeutics, Ingalfarma SA, Monopar Therapeutics, Mundipharma, and Sucampo Pharma; has received research support to his institution from Galera Therapeutics, Novartis, Orogenics, and Sucampo Pharma; and has received stock in Logic Biosciences.

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