Supportive Care in Cancer (2019) 27:3949–3967
https://doi.org/10.1007/s00520-019-04848-4

SPECIAL ARTICLE

Systematic review of basic oral care for the management of oral mucositis in cancer patients and clinical practice guidelines

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Received: 20 January 2019 / Accepted: 30 April 2019 / Published online: 8 July 2019

Abstract

Purpose The aim of this study was to update the clinical practice guidelines for the use of basic oral care (BOC) interventions for the prevention and/or treatment of oral mucositis (OM).

Methods A systematic review was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO). The body of evidence for each intervention in each cancer treatment setting was assigned an evidence level. The findings were added to the database used to develop the 2013 MASCC/ISOO clinical practice guidelines. Based on the evidence level, one of the following three guideline determinations was possible: Recommendation, Suggestion, No guideline possible.

Results A total of 17 new papers across six interventions were examined and merged with a previous database. Based on the literature, the following guidelines were possible. The panel suggests that the implementation of multi-agent combination oral care protocols is beneficial for the prevention of OM during chemotherapy, head and neck (H&N) radiation therapy (RT), and hematopoietic stem cell transplantation (Level of Evidence III). The panel suggests that chlorhexidine not be used to prevent OM in patients undergoing H&N RT (Level of Evidence III). No guideline was possible for professional oral care, patient education, saline, and sodium bicarbonate, and expert opinion complemented these guidelines.

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Conclusions The evidence supports the use of multi-agent combination oral care protocols in the specific populations listed above. Additional well-designed research is needed on the other BOC interventions prior to guideline formulation.

Keywords Basic oral care · Chlorhexidine · Oral mucositis · Sodium bicarbonate · Saline · Patient education · Dental care · Guidelines · Cancer

Introduction

Oral mucositis (OM) is a painful inflammatory, often ulcerative condition; and is a distressing acute side effect of cancer therapy [1]. This condition affects almost all patients undergoing head and neck (H&N) radiation therapy (RT) and 75–100% of hematopoietic stem cell transplant patients (HSCT), with higher occurrence associated with certain conditioning regimens [2–4]. Severe OM may result in the need for enteral or parenteral nutrition and systemic analgesics, increased risk for systemic infections due to the disrupted oral mucosal barrier, unscheduled and prolonged hospital stays as well as interruptions of cancer therapies [2, 5].

The pathophysiology of OM has transitioned from what was understood to be a simple process to a series of interrelated and overlapping events triggered by cancer therapy [6]. The current understanding of OM pathophysiology comprises of five stages: (i) initiation of oral mucosal damage by chemotherapy (CT) or RT, (ii) primary damage from reactive oxygen species generation, (iii) damage amplification due to host inflammation response, (iv) mucosal ulceration as a result of epithelial apoptosis and necrosis, and ultimately followed by (v) healing [6, 7].

There has been a surge in research efforts to discover new and effective interventions for OM. Of these interventions, the employment of Basic Oral Care (BOC) strategies is considered to be the cornerstone of cancer therapy–induced OM management [8–10]. As oral microbiome can stimulate host inflammatory response, many authors have hypothesized that the oral microflora could aggravate OM [11–13]. Thus, the rationale through which BOC strategies may influence OM is the ability to modify oral microbial load which decreases host inflammatory response and subsequently OM severity. However, the precise role of bacterial species in OM pathophysiology is still poorly understood. This is evident from the inconsistent results with the use of antimicrobial therapies in clinical studies to prevent or treat OM [14]. A relatively new concept in OM pathogenesis is the concept of oral flora dysbiosis observed in patients during cancer therapy and how this modulates OM. This has led researchers to suggest exploring interventions aimed to achieve oral flora symbiosis rather than to sterilize the oral cavity with antimicrobial therapies for OM management [11].

The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has published three sets of clinical practice guidelines on BOC strategies for OM [8, 10, 15]. In the first two guidelines published in 2004 and 2007, the use of oral care protocols to reduce cancer therapy–induced OM was suggested [8, 10]. The main difference between the guidelines was that the 2007 guideline provided more details with regard to the elements of BOC strategies [10]. Additionally, the 2007 guidelines [10] formulated recommendations of what constituted good clinical BOC practice for OM management based on the available literature, clinical practice, and expert opinion; not specified in the 2004 guideline [8]. In the 2007 MASCC/ISOO guideline, dental assessment prior to cancer therapy, the use of validated instruments for clinical examination and patient self-report, an interdisciplinary approach to oral care and the implementation and enforcement of a regular and systematic oral care regimen were endorsed based on the evidence available. The oral care regimen involved toothbrushing with a soft toothbrush, regular replacement of toothbrush, flossing, and the use of bland rinses and moisturizers [10].

The growing body of evidence in the recent years allowed the latest 2013 guideline to appraise the effectiveness of specific oral care practices [15]. For clarity, the oral care practices were categorized as follows: (i) oral care protocols, (ii) dental care, (iii) normal saline, (iv) sodium bicarbonate mouthwash, (v) chlorhexidine (CHX) mouthwash, (vi) mixed medication mouthwash, and (vii) calcium phosphate mouthwash [15]. The most significant update of the 2013 guideline was the panel's suggestion not to use CHX in the prevention of OM in adult H&N cancer patients undergoing RT [15].

As part of the comprehensive update of the MASCC/ISOO clinical practice guidelines for the management of cancer treatment–induced OM, the aim of this project was to update the evidence-based clinical practice guidelines for the use of BOC for OM management.

Methods

A search for relevant papers indexed in the literature from Jan 1, 2011 to June 30, 2016 was conducted by two research librarians using Pubmed and Web of Science, with papers selected for review based on defined inclusion and exclusion criteria. The methods including details on the inclusion and

exclusion criteria are described in detail in Ranna et al. [16]. The terms used for the search were generated from the previous versions of the guidelines and are as follows: Artificial saliva, Baking soda, Bland rinse, Calculus, Caregiver education, Chlorhexidine, Dental, Dental care, Dental cleaning, Dental floss, Dentist, Education, Family education, Flossing, Fluoridated, Fluoride, Hygienist, Lip balm, Moisturizer, Mouthcare, Mouthcare protocol/regimen, Mouthwash, Multidisciplinary, Non-medicated rinse, Nurse, Nursing, Nursing oral care/oral hygiene/mouthcare protocol/regimen, Oral bandage, Oral care, Oral care protocol/regimen, Oral decontamination, Oral hygiene, Oral hygiene protocol/regimen, Oral rinse, Oral/mouth/mucositis assessment, Oral/mouth/mucositis examination, Patient education, Plaque, Provider education, Saline, Scaling, Sodium bicarbonate, Staff education, Superoxide dismutase, Toothbrush, Toothbrushing, Toothpaste, and Water.

The papers were reviewed by two independent reviewers and data was extracted using a standard electronic form. Eleven reviewers were recruited from the membership of the Mucositis Study Group, MASCC/ISOO. Studies were scored for their Level of Evidence (LoE) based on the Somerfield criteria [17] and flaws were listed according to Hadorn criteria [18]. A well-designed study was defined as a study with no major flaws per the Hadorn criteria [18].

Findings from the reviewed studies were merged with the evidence from the previous MASCC/ISOO guideline review. Data were integrated into updated guidelines based on the overall LoE. Conclusions were assigned to one of three guideline categories: recommendation, suggestion, or no guideline possible. Guidelines were organized based on the (i) aim of the intervention (OM prevention or treatment) and (ii) treatment modality (RT, CT, chemo-radiotherapy, or high-dose conditioning therapy for HSCT). For the HSCT group, patients undergoing HSCT with or without total body irradiation (TBI) were regarded as a single group. This assumption was made because many authors did not report the OM data separately for HSCT patients receiving TBI versus those who did not; or did not state whether TBI was part of the HSCT protocol.

In this update, the BOC section reviewed the literature for six interventions for the management of OM which were defined as follows:

i) Professional oral care: oral care delivered by dental professionals before or during cancer treatment.
ii) Multi-agent combination oral care protocols: interventions carried out by the patients, lay caregivers and/or non-dental care professionals. The rationale for their implementation is to increase awareness of both patients and staff of the importance of good oral hygiene which may indirectly lead to fewer and less severe oral complications. Typically, protocols involved a multifaceted approach to oral hygiene which includes recommendations with regard to timing, frequency, and products such as combination of varying types of bland mouth rinses, toothbrushes, and flossing procedures.
iii) Patient education: educational interventions designed to help patients understand the importance of oral care and to perform recommended oral practices during cancer therapy.
iv) Saline: saline rinse interventions were compared to other types of bland rinses or CHX rinses.
v) Sodium bicarbonate: sodium bicarbonate diluted in water interventions were compared to other bland rinses or CHX rinses.
vi) CHX: CHX was compared to placebo rinses, bland mouth rinses, or other active agent rinses.

Supersaturated calcium phosphate rinse was removed from the BOC section as this agent would be covered in the MASCC/ISOO publication on Natural and Miscellaneous agents. The literature on mixed medication mouth rinses was reviewed but was excluded as it was not possible to compare between agents due to the heterogeneity of the ingredients.

Results

The Pubmed and Web of Science searches identified 1680 and 761 papers, respectively (Fig. 1). Twenty-seven articles (Pubmed: 25; Web of Science: 2) were retrieved for detailed review. A total of 10 articles were excluded: 7 studies [19–25] were excluded as OM was not an outcome measure in these studies, 1 study evaluated the role of a nurse-practitioner-led clinic which fell outside the inclusion criteria of this review [26], 1 study evaluated oral cryotherapy [27] which is covered in another MASCC/ISOO publication, and the last study [28] was excluded because it was included in the 2013 guideline.

Of the 17 articles that met the inclusion criteria in the current literature search, eight were randomized controlled trials (RCTs). These eight studies examined professional oral care [29], multi-agent combination oral care protocol [30], patient education [31], and use of CHX [32–36]. Tables 1, 2, and 3 provide detailed descriptions of the RCTs from this review and those from the 2013 guideline [15].

Professional oral care

There were three RCTs [29, 37, 38] and six comparative studies of other experimental designs [39–44] that evaluated the benefit of professional oral care for the prevention of OM.

The outcomes assessed were either OM severity or OM-associated pain. Two RCTs [29, 38] and one comparative

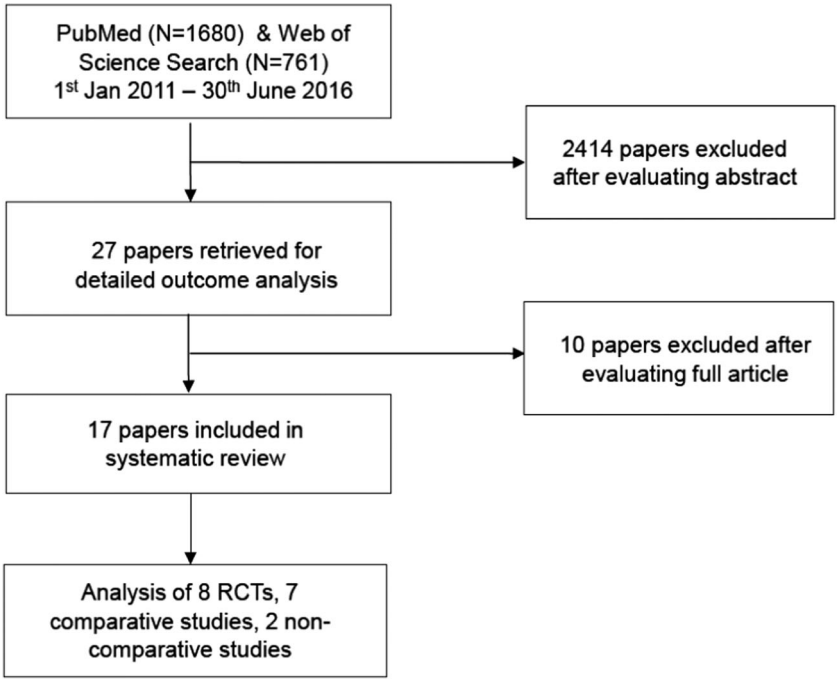

Fig. 1 Review flow diagram. The bottom of the flowchart presents only the new interventional studies from this systematic review. During the review process, these papers were merged with the database of the previous MSG systematic review to cover the entire "literature"

study [43] reported the reduction of OM with professional oral care. The reduction of pain from OM was reported by a single RCT [37] and one comparative study [39] in patients undergoing CT only and chemo-radiotherapy, respectively.

All studies had major flaws and varied considerably with regard to the type of professional oral care delivered, cancer therapy modality, and the patient population studied. No guidelines were possible from these studies. No study looked at the benefit of professional oral care on OM treatment.

Guideline:

- No guideline was possible regarding the use of professional oral care for the prevention of OM for patients with hematologic, solid or H&N cancers due to limited and inconsistent data (LoE: III).
- An expert opinion complements this guideline. Although there was insufficient evidence to support the use of professional oral care for OM prevention, the panel is of the opinion that dental evaluation and treatment as indicated prior to cancer therapy is desirable to reduce the patient's risk for local and systemic infections from odontogenic sources.

Multi-agent combination oral care protocols

In this review, studies were included if the multi-agent combination oral care protocol was evaluated for the purpose of OM management. If the study tested a specific agent while a multi-agent combination protocol was also used, the study's findings would be analyzed under the specific agent that was tested (e.g., professional oral care [37], CHX [66], sodium bicarbonate [62], or micronized sulcrafate [80]). One such example was the study by Djuric et al. In this study, all patients used 0.12% CHX/3% hydrogen peroxide/nystatin 100,000IU mouth rinse 3 times/day. Only the experimental group received dental clearance prior to cancer therapy and additional intensive oral hygiene measures [37]. Thus, this study was included under professional oral care. Studies by Seto et al., Lindquist et al., and Antunes et al. which were previously included in the 2013 guideline review were excluded in this update [81–83]. These studies mentioned the use of oral care protocols in their methods but did not specifically evaluate their use for OM management.

After these exclusions, 5 remaining RCTs [30, 45, 50, 51, 54] evaluating the role of multi-agent combination oral care protocols for the prevention of OM were included. No studies examined the use of protocols for treatment of OM.

i) Patients undergoing CT

DeMorales et al. evaluated the effect of multi-agent combination oral care protocol in children undergoing CT for hematologic cancers, and was the only RCT contributing to the guideline [45]. Another RCT by Kenny et al. did not segregate patients treated with CT with or without TBI and/or total lymphoid irradiation (TLI) thus, no conclusion could be drawn about any specific cancer patient population [50]. In DeMorales et al.'s study, the authors did not demonstrate any benefit with the use of the multi-agent combination oral care protocol for the prevention of OM [45]. However, this finding should be interpreted with caution due to the small

Table 1 Randomized controlled trials (RCTs) reported for basic oral care interventions, overall level of evidence and guideline determination

Basic oral care intervention	Treatment modality	Population	Indication	RCTs author, year	Effectiveness	Overall level of evidence	Guideline category	Guideline statement	Studies of other designs[a]/effectiveness ()
Professional oral care	CT	Hematologic cancer Solid cancer	Prevention	Djuric 2006 [37] Saito 2014 [29]	Y: Pain duration; N: OM severity Y	III	No guideline possible	No guideline was possible with regard to the use of professional oral care for the prevention of OM during CT due to limited and inconsistent data available for each patient population	
	RT & CT	H&N cancer	Prevention	Yoneda 2007 [38]	Y	III	No guideline possible	No guideline was possible with regard to the use of professional oral care for the prevention of OM in H&N cancer patients treated with RT & CT due to limited data	Kubota 2015 [39] — 3(Y), Yokota 2016 [40] — 4(N)
	HSCT	Hematologic cancer	Prevention	–	–		No guideline possible	No guideline was possible with regard to the use of professional oral care for the prevention of OM during HSCT due to lack of RCT and inconsistent data from non-RCT comparative studies	Melkos 2003 [41] — 3(N), Santos 2011 [42] — 3(N), Kashwazaki 2012 [43] — 3(Y), Gurgan 2013 [44] — 4(Y)
Multi-agent combination oral care protocols	CT	Hematologic cancer	Prevention	DeMorales 2001[b] [45]	N	III	Suggestion	The consistent findings from non-RCTs suggest that the implementation of multi-agent combination oral care protocols is beneficial for the prevention of OM during CT	Levy-Polack 1998 [46] — 3(Y), Cheng 2001 [47] — 3(Y), Cheng 2002 [48] — 3(Y), Chen 2004 [49] — 5(Y)
	CT/CT-TBI/CT-TLI	Hematologic cancer	Prevention	Kenny 1990 [50]	N	III	No guideline possible	No guideline was possible with regard to the implementation of multi-agent combination oral care protocols for the prevention of OM during CT with or without TBI/TLI due to the small sample size from a single RCT	
	RT	H&N cancer	Prevention	Shieh 1997 [51] Kartin 2014 [30]	Y Y	III	Suggestion	The implementation of multi-agent combination oral care protocols is beneficial for the prevention of OM during H&N RT	Janjan 1992 [52] — 3(Y)
	HSCT	Hematologic and solid cancers	Prevention	Borowski 1994[c] [54]	Y: OM severity; N: OM onset & duration	III	Suggestion	The implementation of multi-agent combination oral care protocols is beneficial for the prevention of OM during HSCT	Bhatt 2010 [55] — 3(Y), Soga 2010 [28] — 3(Y), Yamagata 2012 [56] — 3(Y), Legert 2014 [57] — 3(Y)
Patient education	HSCT	Hematologic cancer	Prevention	Leppla 2016 [31]	Y-OM severity N-OM incidence	III	No guideline possible	No guideline was possible with regard to the use of patient education for the prevention of OM during HSCT	Schmidt 2016 [58] — 3(N)
	CT	Hematologic cancer	Prevention	–	–		No guideline possible	No guideline was possible with regard to the use of patient education for the prevention of OM during CT due to limited data	Yavuz 2015[b] [59] — 5(Y)
Saline	RT	Not stated (likely H&N cancer)	Prevention	Feber 1996 [60]	Y: OM onset; N: OM severity	III	No guideline possible	No guideline was possible with regard to the use of saline rinse over hydrogen peroxide for the prevention of OM during H&N RT due to limited data	
	HSCT	Not stated (likely hematologic cancer)	Prevention	Vokurka 2005 [61]	N	III	No guideline possible	No guideline was possible with regard to the use of saline rinse over povidone iodine for the prevention of OM during HSCT due to limited data	
Sodium bicarbonate	CT	Hematologic cancer	Prevention	Choi 2012 [33]	Y: OM severity & pain severity; N: OM incidence & duration	III	No guideline possible	No guideline was possible with regard to the use of sodium bicarbonate rinse over chlorhexidine for the prevention of OM during CT due to limited data	

Table 1 (continued)

Basic oral care intervention	Treatment modality	Population	Indication	RCTs author, year	Effectiveness	Overall level of evidence	Guideline category	Guideline statement	Studies of other designs[a]/effectiveness ()
	RT	H&N cancer	Prevention	Dudjak 1987 [62]	N	III	No guideline possible	No guideline was possible with regard to the use of sodium bicarbonate rinse over hydrogen peroxide for the prevention of OM during H&N RT due to limited data	
Chlorhexidine versus placebo	CT	Hematologic cancer	Prevention	McGaw 1985 [63]	Y	III	No guideline possible	No guideline was possible with regard to the use of chlorhexidine in the prevention of OM during CT due to conflicting results	Costa[b] 2003 [85] — 3(Y)
		Hematologic and solid cancers		Ferretti 1990[c] [64]	Y				
		Hematologic and solid cancers		Rutkauskas 1993 [65]	N				
		Solid cancer		Dodd 1996 [66]	N				
		Solid cancer		Sorensen 1998 [67]	Y				
	RT & CT	H&N cancer	Prevention	Diaz-Sanchez 2015 [32]	N	III	No guideline possible	No guideline was possible with regard to the use of chlorhexidine in the prevention of OM in H&N cancer patients treated with RT and CT due to limited data	
	RT	H&N cancer	Prevention	Spijkervet 1989 [68]	N	III	Suggestion	The use of chlorhexidine is not suggested for the prevention of OM during H&N RT	
		Hematologic and solid cancers		Ferretti 1990[c] [64]	N				
		Not stated (likely H&N cancer)		Foote 1994 [69]	N				
	HSCT	Hematologic cancer and non-neoplastic conditions	Prevention	Ferretti 1988[c] [70]	Y	III	No guideline possible	No guideline was possible with regard to the use of chlorhexidine in the prevention of OM during HSCT due to conflicting results	
		Hematologic and solid cancers		Raether 1989[b] [71]	N				
		Hematologic and solid cancers		Weisdorf 1989[c] [72]	N				
		Hematologic and solid cancers		Rutkauskas 1993 [65]	Y				
Chlorhexidine versus active agents (single or multiple arms)	CT	Solid cancer	Prevention	Sorensen 1998 [67]	Y	III	No guideline possible	No guideline was possible with regard to the use of chlorhexidine over other agents (sodium bicarbonate, amine stannous fluoride, zinc sulfate, benzydamine) for the prevention of OM during CT due to limited data available for each intervention	
		Hematologic and solid cancers		Pitten 2003 [73]	N				
		Hematologic and solid cancers		Cheng 2004[b] [74]	Y				
		Hematologic cancer		Mehdipour 2011 [34]	N				
		Hematologic cancer		Choi 2012 [33]	N				
	CT	Hematologic and solid cancers	Treatment	Dodd 2000 [75]	N	III	No guideline possible	No guideline was possible with regard to the use of chlorhexidine for the treatment of OM during CT	
	RT	H&N cancer	Prevention	Samaranayake 1998 [76]	N	III	No guideline possible	No guideline was possible with regard to the use of chlorhexidine over other	

Table 1 (continued)

Basic oral care intervention	Treatment modality	Population	Indication	RCTs author, year	Effectiveness	Overall level of evidence	Guideline category	Guideline statement	Studies of other designs[a]/effectiveness ()
				Cheng 2006 [77]	N			agents (sodium bicarbonate/saline, saline, benzydamine and povidone iodine) for the prevention of OM during H&N RT due to limited data available for each intervention	
				Madan 2008 [78]	N				
	RT	H&N cancer	Treatment	Roopashri 2011 [36]	N	III	No guideline possible	No guideline was possible with regard to the use of chlorhexidine for the treatment of OM during H&N RT due to limited data	
	CT or HSCT	Hematologic cancer	Prevention	Epstein 1992 [79]	N	III	No guideline possible	No guideline was possible with regard to the use of chlorhexidine over saline or nystatin for the prevention of OM during HSCT due to limited data	
	HSCT	Hematologic cancer	Prevention	Mutters 2015 [35]					

CT chemotherapy, *RT* radiotherapy, *HSCT* hematopoietic stem cell transplantation, *TBI* total body irradiation, *TLI* total lymphoid irradiation

[a] Non-RCT related to the respective intervention were considered as supporting evidence, when applicable; the weight of the non-RCT type studies was following the methods of the MASCC/ISOO mucositis study group. 1. Meta-analysis, 2. RCT, 3. Non-RCT, 4. Cohort, 5. Before and after, 6. Case control studies, 7. Cross sectional, 8. Case series, 9. Case report, 10. Expert opinion

[b] Pediatric population only

[c] Mixed adult and pediatric populations

sample size ($n = 12$). Notwithstanding, these studies were conducted in pediatric patient populations. In view of four other comparative trials that demonstrated the benefit of multi-agent combination oral care protocols in reducing OM severity, it is suggested that the oral care protocols should be performed to create an atmosphere of awareness and compliance for the prevention of OM during CT in children [46–49].

Guideline:

- The panel suggests that implementation of multi-agent combination oral care protocols is beneficial for the prevention of OM during CT (LoE III).

ii) Patients undergoing H&N RT

Two RCTs evaluated the use of multi-agent combination oral care protocols in preventing OM in patients undergoing H&N RT [30, 51]. Although both studies evaluated similar population of patients, the protocols by type of mouth rinse and timing of implementation during therapy varied between studies. Regardless, both studies consistently found a significant reduction in OM severity and duration in patients in the multi-agent combination oral care protocol group compared to the control group.

Guideline:

- The panel suggests that implementation of multi-agent combination oral care protocols is beneficial for the prevention of OM during H&N RT (LoE III).

iii) Patients undergoing HSCT

The RCT by Borowski et al. [54] and four comparative studies with other experimental designs [28, 55–57] all demonstrated significant reduction of OM incidence and severity in patients undergoing HSCT with the use of multi-agent combination oral care protocols. However, this benefit was not consistently noted for reduction of pain severity.

Guideline:

- The panel suggests that implementation of multi-agent combination oral care protocols is beneficial for the prevention of OM during HSCT (LoE III).

Patient education

Patient education as an intervention for OM prevention during cancer therapy is a new intervention added to this guideline update. Three new studies, one RCT [31] and two comparative studies [58, 59] were retrieved. These studies evaluated the benefits of patient education on oral care practices during

Table 2 Randomized controlled trials (RCTs) reported for effectiveness for oral mucositis (OM)

Basic oral care intervention	Treatment modality	Population	Indication	RCTs author, year	Effectiveness[c]				
					OM incidence/severity	OM duration	Pain severity	Pain duration	Quality of life measures
Professional oral care	CT	Hematologic cancer	Prevention	Djuric 2006 [37]	N (severity)		Y		
		Solid cancer		Saito 2014 [29]	Y (incidence & severity)				
	RT & CT	H&N cancer		Yoneda 2007 [38]	Y (incidence)				
Multi-agent combination oral care protocols	CT	Hematologic cancer	Prevention	DeMorales 2001b[a] [45]	N (incidence)				
	CT/CT-TBI/CT-TLI	Hematologic cancer	Prevention	Kenny 1990 [50]	N (incidence)				
	RT	H&N cancer	Prevention	Shieh 1997 [51]	Y (incidence)	Y (onset)	Y		Y (OAG score)
				Kartin 2014 [30]	Y (severity)	Y (onset)			
	HSCT	Hematologic and solid cancers	Prevention	Borowski 1994[b] [54]	Y (severity)	N (onset & duration)			
Patient education	HSCT	Hematologic cancer	Prevention	Leppla 2016 [31]	Y (severity) N (incidence)				
Saline	RT	Not stated (likely H&N cancer)	Prevention	Feber 1996 [60]	N (severity)	Y (onset)			
	HSCT	Not stated (likely hematologic cancer)	Prevention	Vokurka 2005 [61]	N (incidence & severity)	N (onset & duration)	N		
Sodium bicarbonate	CT	Hematologic cancer	Prevention	Choi 2012 [33]	Y (severity) N (incidence)	N (duration)	Y		
	RT	H&N cancer	Prevention	Dudjak 1987 [62]					N (mouth comfort)
Chlorhexidine versus placebo	CT	Hematologic cancer	Prevention	McGaw 1985 [63]	Y (severity)	Y			
		Hematologic and solid cancers		Ferretti 1990[b] [64]	Y (incidence & severity)	Y (duration)			
		Hematologic and solid cancers		Rutkauskas 1993 [65]	N (severity)				
		Solid cancer		Dodd 1996 [66]	N (incidence & severity)	N (onset)			
		Solid cancer		Sorensen 1998 [67]	Y (incidence & severity)	Y (duration)			
	RT & CT	H&N cancer	Prevention	Diaz-Sanchez 2015 [32]	N (severity)		N		
	RT	H&N cancer	Prevention	Spijkervet 1989 [68]	N (incidence & severity)				
		Hematologic and solid cancers		Ferretti 1990[b] [64]	N (incidence & severity)	N			
		Not stated (likely H&N cancer)		Foote 1994 [69]	N (severity)	N			
	HSCT	Hematologic cancers and non-neoplastic conditions	Prevention	Ferretti 1988[b] [70]	Y (incidence & severity)	Y (onset)			
		Hematologic and solid cancers		Raether 1989[a] [71]	N (severity)				
		Hematologic and solid cancers		Weisdorf 1989[b] [72]	N (severity)		N		
		Hematologic and solid cancers		Rutkauskas 1993 [65]	Y (severity)	Y			
Chlorhexidine versus active agents (single or multiple arms)	CT	Solid cancer	Prevention	Sorensen 1998 [67]	Y (incidence & severity)	Y (duration)			
		Hematologic and solid cancers		Pitten 2003 [73]	N (severity)				
		Hematologic and solid cancers		Cheng 2004[a] [74]	Y (incidence & severity)				
		Hematologic and solid cancers		Mehdipour 2011 [34]	N (severity)				
		Hematologic cancer		Choi 2012 [33]	N (incidence & severity)	N	N		
	CT	Hematologic and solid cancers	Treatment	Dodd 2000 [75]		N (duration)	N	N	
	RT	H&N cancer	Prevention	Samaranayake 1998 [76]	N (severity)		N		
				Cheng 2006 [77]	N (severity)		N		
				Madan 2008 [78]	N (severity)	N (onset)			
	RT	H&N cancer	Treatment	Roopashri 2011 [36]	N (incidence & severity)	N (onset)	N		
	CT or HSCT	Hematologic and solid cancers	Prevention	Epstein 1992 [79]	N (severity)				
	HSCT	Hematologic cancer		Mutters 2015 [35]	N (severity)				

CT chemotherapy, *RT* radiotherapy, *HSCT* hematopoietic stem cell transplantation, *TBI* total body irradiation, *TLI* total lymphoid irradiation, *OAG* oral assessment guide

[a] Pediatric population only

[b] Mixed adult and pediatric populations

[c] Additional parameters that were reported in these studies were outside the scope of this table

Table 3 Details of interventions of randomized controlled trials (RCTs)

Basic oral care intervention	Treatment modality	Population	Indication	RCTs author, year	Effectiveness	Intervention group	Control/comparative group
Professional oral care	CT	Hematologic cancer	Prevention	Djuric 2006 [37]	Y: Pain duration; N: OM severity	• Pre-CT dental care[c] • Intensive oral hygiene[c]: Patients provided with toothbrushes with round-ended soft nylon bristles, and instructed in oral hygiene measures including frequency and technique of toothbrushing (modified Stillman method) • During CT: Patients were motivated for intensive oral hygiene and to continue tooth brushing if able to tolerate, unless not directed by hematologist. If difficulties with toothbrushing, patients advised to remove dental deposits with cotton buds • The above oral hygiene measures were supervised by nurses and assisted if needed • Use of mouth rinses 3 times/day with 0.12% chlorhexidine mixed with 3% hydrogen peroxide and nystatin 100,000IU (Common to both groups)	• No pre-CT dental care • Patients maintained their usual oral hygiene without interference from nurses
		Solid cancer		Saito, 2014 [29]	Y	• Prior to the start of CT and at the time of the first CT administration, patients were interviewed in the usual manner, assessed and given instructions on brushing, nutrition, and lifestyle (Common to both groups) • The interviews, assessments, and advice repeated after the second cycle of CT • Patients received weekly professional oral health care (POHC) consisting of scaling and polishing • During weekly POHC, the status of the oral cavity determined, and further guidance given base on this determination • Reassessment performed in the second week after CT initiation	• POHC only instituted if patients exhibited symptoms of OM
	RT & CT	H&N cancer	Prevention	Yoneda 2007 [38]	Y	• Pre-cancer dental care included supragingival scaling of all teeth with an ultrasonic scaler and guidance regarding oral hygiene, including dental brushing by a dentist performed (Common to both groups) • Patients preformed dental brushing with a dental brush after meals (Common to both groups) • Patients received oral care with a dental brush by a dentist in combination with irrigation and suctioning for 15 min 3 days/week for 2–4 weeks between 7 pm and 8 pm after dinner • At this time, 20 ml of 0.5% povidone-iodine mouthwash was also used by both dentist and patients	
Multi-agent combination oral care protocols	CT	Hematologic cancer	Prevention	DeMorales 2001[a] [45]	N	• Pre-CT dental care[c] (Common to both groups) • Reinforce oral physiotherapy throughout CT • Detection (by fuscin) and removal of bacterial plaque • Before and after CT: use of 0.05% sodium fluoride mouthwash 3 times/day, topical 20% myconazole oral gel after each mouthwash, use of fluoridated toothpaste 4 times/day • During CT: Toothpaste substituted with sodium bicarbonate	• Oral physiotherapy only (no details given)

Table 3 (continued)

Basic oral care intervention	Treatment modality	Population	Indication	RCTs author, year	Effectiveness	Intervention group	Control/comparative group
	CT +/− TBI/TLI	Hematologic cancer	Prevention	Kenny 1990 [50]	N	• Lip: Non-occlusive preparation of lanolin and aloe vera	• Lip: Vitamin A and D ointment in lanolin petrolatum base
						• Oral lubricant: Sterile mint flavored toothette premoistened with aloe vera and chlorophyll	• Oral lubricant: 0.9% sodium chloride solution
						• Cleanser: Toothette premoistened with sodium bicarbonate	• Cleanser: Dry sterile mint flavored toothette
						• Mouthwash: 0.9% sodium bicarbonate	• Mouthwash: 0.9% sodium chloride solution
	RT	H&N cancer	Prevention	Shieh 1997 [51]	Y	• Experimental group 1 (E1): Oral care instructions[c] started on Day 1 of RT - Toothbrush type, toothbrushing frequency and technique (Bass) specified - Rinse with sterile water each meal and at bedtime; avoid use of commercial mouthwashes, smoking, chewing betel nuts, hot temperature and spicy foods, alcohol - Denture care - Lip care with petroleum jelly	• Control group (no details given)
						• Experimental group 2: Oral care instructions[c] (same as E1) started 1 week before RT	
				Kartin 2014 [30]	Y	• Evaluate mouth health for 1 week using the mouth evaluation guidelines or have a dentist perform an examination if necessary • Oral hygiene care[c] - Toothbrush type, toothbrushing frequency and technique specified - Floss after meals if blood levels are not low - Tongue hygiene - Oral care solutions or water rinses after meals and before bed, and if awoken during the night. Gargle 4 times/day at specified times of day, with 1 teaspoon (tsp) of baking soda and 1 tsp. of salt in 200 ml of boiled and cooled water - Denture care: Take out and clean dentures after meals. Before bed, take out dentures and store in saline or a mixture of water/sodium bicarbonate • Xerostomia: Chew sugar-free mint gum or suck on ice chips. Avoid alcohol, lemon and glycerin products • Dry and cracked lips: Use soft paraffin, cold cream, water-based balm	• Oral care including sodium bicarbonate rinses 4 times/day
	HSCT	Hematologic and solid cancers	Prevention	Borowski 1994[b] [54]	Y: OM severity; N: OM onset & duration	• Chlorhexidine mouthwash at least 5 times/day (Common to both groups) • Initial dental treatment[c]	• Dental treatment only provided in a life-threatening dental infection

Table 3 (continued)

Basic oral care intervention	Treatment modality	Population	Indication	RCTs author, year	Effectiveness	Intervention group	Control/comparative group
						• During HSCT: Toothbrushing (Bass or Charters technique) and gum brushing with a toothbrush at least 3 times/day after meals. Toothbrushing discontinued if uncontrollable gum bleeding • Instructions provided by dentist	• Toothbrushing and gingival brushing
Patient education	HSCT	Hematologic cancer	Prevention	Leppla 2016 [31]	Y: OM severity; N: OM incidence	• Educational, cognitive and behavioral counseling over 2 sessions - Oral mucositis assessment - Self-assessment (pediatric oral mucositis daily questionnaire) - Brushing technique (modified Bass) - Frequencies of rinses - Written materials • The above was in addition to usual care given in control group	• Patient provided with an oral hygiene information sheet and a list of mouth rinses (chlorhexidine, sage infusion, saline) to use • Dose and timing of care inconsistent
Saline	RT	Not stated (likely H&N cancer)	Prevention	Feber 1996 [60]	Y: OM onset; N: OM severity	Saline	Hydrogen peroxide
	HSCT	Not stated (likely hematologic cancer)	Prevention	Vokurka 2005 [61]	N	Saline	Diluted povidone iodine (1 ml Betadine/100 ml)
Sodium bicarbonate	CT	Hematologic cancer	Prevention	Choi 2012 [33]	Y: OM severity & pain severity N: OM incidence & duration	1% sodium bicarbonate	0.1% chlorhexidine
	RT	H&N cancer	Prevention	Dudjak 1987 [62]	N	• Denture care, toothbrush, floss, fluoride carrier for 5 min/day, petroleum jelly to lip as necessary (Common to both groups) • Performed every 4 h when awake (Common to both groups) • Sodium bicarbonate (2 teaspoon to 1 quart water), swish for 1 min or as long as tolerable	• Hydrogen peroxide (½ cup hydrogen peroxide to ½ cup water), swish for 1 min or as long as tolerable
Chlorhexidine versus placebo	CT	Hematologic cancer	Prevention	McGaw 1985 [63]	Y	0.1% chlorhexidine	Placebo
		Hematologic and solid cancers		Ferretti 1990[b] [64]	Y	0.12% chlorhexidine	Placebo
		Hematologic and solid cancers		Rutkauskas 1993 [65]	N	0.12% chlorhexidine	Placebo
		Solid cancer		Dodd 1996 [66]	N	0.12% chlorhexidine	Sterile water
		Solid cancer		Sorensen 1998 [67]	Y	0.1% chlorhexidine	Saline
	RT & CT	H&N cancer	Prevention	Diaz-Sanchez 2015 [32]	N	0.2% chlorhexidine	Placebo

Table 3 (continued)

Basic oral care intervention	Treatment modality	Population	Indication	RCTs author, year	Effectiveness	Intervention group	Control/comparative group
	RT	H&N cancer	Prevention	Spijkervet 1989 [68]	N	0.1% chlorhexidine	Placebo
		Hematologic and solid cancers		Ferretti 1990[b] [64]	N	0.12% chlorhexidine	Placebo
		Not stated (likely H&N cancer)		Foote 1994 [69]	N	Chlorhexidine (concentration not stated)	Placebo
	HSCT	Hematologic cancer and non-neoplastic conditions	Prevention	Ferretti 1988[b] [70]	Y	0.12% chlorhexidine	Placebo
		Hematologic and solid cancers		Raether 1989[a] [71]	N	0.12% chlorhexidine	Placebo
		Hematologic and solid cancers		Weisdorf 1989[b] [72]	N	0.12% chlorhexidine	Placebo
		Hematologic and solid cancers		Rutkauskas 1993 [65]	Y	0.12% chlorhexidine	Placebo
Chlorhexidine versus active agents (single or multiple arms)	CT	Solid cancer	Prevention	Sorensen 1998 [67]	Y	0.1% chlorhexidine	Cryotherapy
		Hematologic and solid cancers		Pitten 2003 [73]	N	0.3% chlorhexidine/96% ethanol/30% hydrogen peroxide	Amine stannous fluoride
		Hematologic and solid cancers		Cheng 2004[a] [74]	Y	Chlorhexidine (concentration not stated)	Benzydamine
		Hematologic cancer		Mehdipour 2011 [34]	N	0.2% chlorhexidine	0.2% zinc sulfate
		Hematologic cancer		Choi 2012 [33]	N	0.1% chlorhexidine	1% sodium bicarbonate
	CT	Hematologic and solid cancers	Treatment	Dodd 2000 [75]	N	0.12% chlorhexidine	• Magic mouthwash • Salt/sodium bicarbonate
	RT	H&N cancer	Prevention	Samaranayake 1998 [76]	N	0.2% chlorhexidine	0.15% benzydamine
				Cheng 2006 [77]	N	0.2% chlorhexidine	0.15% benzydamine
				Madan 2008 [78]	N	0.12% chlorhexidine	• 1% povidone iodine • Salt/sodium bicarbonate • Water
	RT	H&N cancer	Treatment	Roopashri 2011 [36]	N	0.2% chlorhexidine	• 0.15% benzydamine • 5% povidone iodine • Distill water

Table 3 (continued)

Basic oral care intervention	Treatment modality	Population	Indication	RCTs author, year	Effectiveness	Intervention group	Control/comparative group
	CT or HSCT	Hematologic cancer	Prevention	Epstein 1992 [79]	N	0.2% chlorhexidine	• Nystatin 100,000IU • 0.2% chlorhexidine/nystatin 100,000IU • Saline
	HSCT	Hematologic cancer	Prevention	Mutters 2015 [35]		0.1% chlorhexidine	0.1% octenidine -dihydrochloride

CT chemotherapy, *RT* radiotherapy, *HSCT* hematopoietic stem cell transplantation, *TBI* total body irradiation, *TLI* total lymphoid irradiation

[a] Pediatric population only

[b] Mixed adult and pediatric populations

[c] Please refer to the paper for more details

cancer therapy and empowering patients to manage their own daily oral care. All studies involved delivering specialized single or multiple training sessions by trained personnel such as dentists and oncology nurses to patients prior to initiation of cancer therapy [31, 58, 59]. In two studies, patients also performed daily self-assessments of their oral conditions during cancer therapy [58, 59].

The patient population for the studies were patients with hematologic cancers — two were on HSCT patients [31, 58] and the other included patients undergoing CT [59]. Leppla et al. [31] reported that patient education resulted in a significant reduction of OM severity in HSCT patients, while the comparative study by Schmidt et al. [58] in the same population found no benefit. To note, a potential confounder in the Schmidt et al.'s study was the use of palifermin only in the control group. Yavuz et al. assessed hematologic cancer patients who were undergoing CT and found a significant benefit of patient education for minimizing OM severity and pain [59]. None of the education studies provided adequate theoretical support for the educational intervention and lack of fidelity to the intervention was a confounder. There were no studies on OM treatment.

Guideline:

- No guideline was possible regarding the use of patient education for the prevention of OM in hematologic cancer patients during HSCT or CT due to limited and inconsistent data (LoE: III).
- An expert opinion complements this guideline. The panel is of the opinion that educating patients about the benefits of BOC strategies is still appropriate as this may improve patient's self-management and adherence to the recommended oral care protocol during cancer treatment.

Bland mouth rinses

Studies of bland mouth rinses included regimens using saline and/or sodium bicarbonate for OM management. This review excluded studies that evaluated bland mouth rinses if they were components of a multi-combination oral care agent protocol, as it was not possible to draw specific conclusions about efficacy of the rinses. Only studies comparing saline and/or sodium bicarbonate with other bland mouth rinses or CHX were included in the bland mouth rinse recommendations. All studies reviewed evaluated these agents for the prevention of OM; there were no studies examining OM treatment.

i. Saline

Two RCTs evaluated the use of saline for the prevention of OM. Feber et al. compared saline rinse with hydrogen peroxide in H&N RT patients and found that saline reduced OM severity [60]. Vokurka et al. [61] compared saline rinse with povidone iodine in patients undergoing HSCT and found no benefit for OM management.

ii. Sodium bicarbonate

Two RCTs evaluated the use of sodium bicarbonate for the prevention of OM; one study compared 1% sodium bicarbonate with 0.1% CHX in patients undergoing CT for hematologic cancers [33]; the other compared sodium bicarbonate with 1.5% hydrogen peroxide in H&N RT patients [62]. While the former demonstrated that sodium bicarbonate reduced OM severity over CHX, the latter study found that sodium bicarbonate had no benefit for OM management.

Guideline:

- No guideline was possible regarding the use of saline or sodium bicarbonate rinses in the prevention or treatment of OM in patients undergoing cancer therapy due to limited data for each intervention (LoE III).
- An expert opinion complements this guideline. Despite the limited data available for both saline and sodium bicarbonate, the panel recognizes that these rinses are inert bland rinses that increase oral clearance which may be helpful for maintaining oral hygiene and improving patient comfort.

Chlorhexidine

Chlorhexidine has been studied more rigorously than any other oral agent; with multiple RCTs [32–36, 63–79] evaluating the use of CHX for OM management. In this review, the studies were divided into those that compared CHX with a placebo or bland agent (e.g., saline, sterile water) [32, 63–72] and those that compared CHX with an active agent (e.g., benzydamine) [33–36, 67, 73–79]. The specific comparator in each study is listed in Table 3. The results of the literature search found one new RCT evaluating the efficacy of CHX with placebo [32] and four new RCTs [33–36] evaluating the efficacy of CHX to several other active agents. Due to the heterogeneity of the populations studied, varied indications for OM management and the diversity of the active agents used for comparisons against CHX, it was difficult to draw any conclusions from these studies.

Considering all the available data, the benefits of CHX over placebo/bland agents or active agents for the prevention of OM in patients undergoing cancer therapy were conflicting or limited with the exception of those undergoing H&N RT. The three RCTs that evaluated CHX in H&N cancer patients treated with RT [64, 68, 69] showed no additional benefit of CHX over placebo for the prevention of OM. In fact, Foote et al. reported significantly more discomfort, taste alteration

and teeth staining with the use of CHX [69]. The CHX concentrations used in these studies were 0.1% [68], 0.12% [64], or not stated [69].

Guideline:

- The panel suggests that CHX not be used in the prevention of OM in patients undergoing H&N RT (LoE III).
- No guideline was possible with regard to the use of CHX for the prevention of OM in all other cancer populations due to conflicting or limited data (LoE III).

Only two RCTs evaluated CHX use in OM treatment [36, 75]. The results were not comparable between studies as both studies evaluated the use of CHX with different agents in different populations.

Guideline:

- No guideline was possible regarding the use of CHX for the treatment of OM in all cancer populations due to conflicting or limited data (LoE III).

Discussion

This review was conducted for the purpose of updating the 2013 MASCC/ISOO BOC guideline and represents a thorough review of the literature and a summary of the evidence to date. BOC remains an important best practice for patients undergoing cancer treatments; however, as a research area, there is limited evidence from high-quality, rigorous studies.

The guideline for multi-agent combination oral care protocols to prevent OM remains unchanged from the 2013 guideline [15]. A ubiquitous commonality among several of the oral care protocols was the advocation of regular assessment of OM and tooth brushing during cancer therapy. This concurs with the literature suggesting continuing brushing teeth during cancer therapy, and that pancytopenia is not a contraindication [15, 84]. Additional studies retrieved in the current literature search allowed a higher level of detail in that the panel was able to specify the guideline for patients undergoing CT, H&N RT, and HSCT in this update. However, it was evident that there continues to be a vast heterogeneity in protocols between studies, making it difficult to draw conclusions about the superiority of any one multi-agent combination oral care protocol. The heterogeneity is attributed to the agents used in the protocols as well as differences in timing, frequency, intensity, equipment, and storing conditions, which are contributing factors in reproducing the protocol. Additionally, there was a lack of standardized vocabulary and detail stated in many studies. This was particularly pertinent with regard to the use of the term "magic mouthwash" whereby the concentration and proportion of the active ingredients were often ambiguous.

Consistent with the previous guideline, the panel continues to encourage the use of bland rinses. Rinses increase oral clearance of debris, promote oral hygiene, and improve patient comfort during cancer therapy. Since the literature search, a new RCT published in early 2018 compared 5% sodium bicarbonate to 0.12% CHX and *Plantago major* extract. The study found that patients on the 5% sodium bicarbonate daily healed faster from OM than the other groups but the benefit was not statistically significant [86]. This new evidence did not change the panel's decision.

The suggestion that CHX not be used in patients undergoing H&N RT for the prevention of OM is unchanged from the previous guideline [15] as no new evidence was retrieved related to this patient population. It is important to emphasize that the panel's recommendation to not use CHX is specific to the prevention of OM and excludes other conditions whereby CHX is indicated, for example in oral infections.

Several new studies on patient education [31, 58, 59] and professional oral care [29, 39, 40, 42–44] were retrieved in this review. Although no guideline was possible for these interventions due to conflicting and limited evidence, generally positive findings suggest further investigations into the potential benefit of these measures for OM management are warranted. The panel's expert opinion is that patient education is an integral part of patient care and should be extended to OM care. This recommendation is supported by two new studies evaluating patient education and quality of life in cancer patients with OM. Although these new studies were not designed to capture the effects of patient education on OM prevention, both demonstrated a trend toward a significantly higher quality of life in patients in the education group compared to those in the control group [53, 87]. The benefits of patient education for OM self-management is based on the rationale that increased knowledge and awareness allows patients to be more empowered and involved in their oral care. This would facilitate the attainment of desired patient behaviors (e.g., increased adherence to oral care regimens). With regard to professional oral care, no guideline was possible for OM specifically. There is no intention to claim that professional oral care treatment prior to cancer therapy is not warranted from the standpoint of minimizing or eradicating potential infections from odontogenic sources.

This systematic review stresses the importance of a multidisciplinary effort where medical, dental, and nursing professionals as well as patients collaborate to formulate a clinical pathway for cancer therapy–associated OM in the respective institutions. We advise to augment the guideline from this review within a clinical care pathway to facilitate communication and delivery of care.

In summary, this update identified new data that supported and detailed the previous guidelines for BOC. Likewise, this guideline update added a new category of intervention, namely patient education that may contribute to OM prevention.

Acknowledgements The authors would like to gratefully acknowledge Mr. Eyal Zur, BSc Pharm, RPh, MBA, for the calculations of the hydrogen peroxide and sodium bicarbonate concentrations under the bland mouth rinses in the results section.The authors are also thankful for the medical librarians for their valuable contribution to this project: Lorraine Porcello, MSLIS, MSIM – Bibby Dental Library, Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY, USA; Daniel A. Castillo, MLIS – Edward G. Miner Library, University of Rochester Medical Center, Rochester, NY, USA.

Compliance with ethical standards

Conflict of interest Per the MASCC Guidelines Policy, employees of commercial entities were not eligible to serve on this MASCC Guidelines Panel. The following authors disclose no conflict of interest (CHLH, LAG, JF, KKFC, AK, DG, JMFD, JJ, SA, TK, DW, JE, VR, AV, SE). PB has served an advisory role for AstraZeneca, Helsinn, and Kyowa Kyrin and received grants from Merck, Kyowa Kyrin, and Roche. 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, Oragenics, and Sucampo Pharma; and has received stock in Logic Biosciences.

References

1. Bellm LA, Epstein JB, Rose-Ped A, Martin P, Fuchs HJ (2000) Patient reports of complications of bone marrow transplantation. Support Care Cancer 8(1):33–39
2. Elting LS, Cooksley CD, Chambers MS, Garden AS (2007) Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys 68(4):1110–1120
3. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, Bekele BN, Raber-Durlacher J, Donnelly JP, Rubenstein EB, for the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (2004) Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 100(9 Suppl):1995–2025
4. Robien K, Schubert MM, Bruemmer B, Lloid ME, Potter JD, Ulrich CM (2004) Predictors of oral mucositis in patients receiving hematopoietic cell transplants for chronic myelogenous leukemia. J Clin Oncol 22(7):1268–1275
5. Lalla RV, Saunders DP, Peterson DE (2014) Chemotherapy or radiation-induced oral mucositis. Dent Clin N Am 58(2):341–349
6. Al-Dasooqi N, Sonis ST, Bowen JM, Bateman E, Blijlevens N, Gibson RJ, Logan RM, Nair RG, Stringer AM, Yazbeck R, Elad S, Lalla RV (2013) Emerging evidence on the pathobiology of mucositis. Support Care Cancer 21(7):2075–2083
7. Sonis ST (2004) Pathobiology of mucositis. Semin Oncol Nurs 20(1):11–15
8. Rubenstein EB, Peterson DE, Schubert M, Keefe D, McGuire D, Epstein J, Elting LS, Fox PC, Cooksley C, Sonis ST (2004) Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 100(9 Suppl):2026–2046
9. Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, McCabe MG, Meyer S, Khalid T (2010) Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev (12):CD000978
10. Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, Migliorati CA, McGuire DB, Hutchins RD, Peterson DE, (2007) for the mucositis study section of the multinational association of supportive care in cancer, and the international society for oral oncology, updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 109(5):820–831
11. Stringer AM, Logan RM (2015) The role of oral flora in the development of chemotherapy-induced oral mucositis. J Oral Pathol Med 44(2):81–87
12. Vasconcelos RM, N Sanfilippo, Paster BJ, Kerr AR, Li Y, Ramalho L, Queiroz EL, Smith B, Sonis ST, & Corby PM (2016) Host-microbiome cross-talk in Oral mucositis. J Dent Res 95(7):725–733
13. Vanhoecke B, de Ryck T, Stringer A, van de Wiele T, Keefe D (2015) Microbiota and their role in the pathogenesis of oral mucositis. Oral Dis 21(1):17–30
14. Lalla RV, Sonis ST, Peterson DE (2008) Management of oral mucositis in patients who have cancer. Dent Clin N Am 52(1):61–77 viii
15. McGuire DB, Fulton JS, Park J, Brown CG, Correa ME, Eilers J, Elad S, Gibson F, Oberle-Edwards LK, Bowen J, Lalla RV (2013) Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer 21(11):3165–3177
16. Ranna V, Cheng K, Castillo D, Porcello L, Vaddi A, Lalla R, Bossi P, Elad S (2019) Development of the MASCC/ISOO clinical practice guidelines for mucositis: an overview of the methods support care. Support Care Cancer https://doi.org/10.1007/s00520-019-04891-1
17. Somerfield M, Padberg J, Pfister D, Bennett C, Recht A, Smith T, Weeks J, Winn R, Duraant J (2000) ASCO clinical practice guidelines: process, progress, pitfalls, and prospects. Classic Papers and Current Comments 4:881–886
18. Hadorn DC, Baker D, Hodges JS, Hicks N (1996) Rating the quality of evidence for clinical practice guidelines. J Clin Epidemiol 49(7):749–754
19. Coke L, Otten K, Staffileno B, Minarich L, Nowiszewski C (2015) The impact of an oral hygiene education module on patient practices and nursing documentation. Clin J Oncol Nurs 19(1):75–80
20. Lanzos I, Herrera D, Lanzós E, Sanz M (2015) A critical assessment of oral care protocols for patients under radiation therapy in the regional University Hospital Network of Madrid (Spain). J Clin Exp Dent 7(5):e613–e621
21. Tringali CA, Kanaskie ML (2012) Measuring the impact of an educational program on nurses: teaching an evidence-based approach to oral mucositis. J Nurses Staff Dev 28(6):E1–E4
22. Morais MO, Elias MRA, Leles CR, Dourado Pinezi JC, Mendonça EF (2016) The effect of preventive oral care on treatment outcomes of a cohort of oral cancer patients. Support Care Cancer 24(4):1663–1670
23. Qutob AF, Allen G, Gue S, Revesz T, Logan RM, Keefe D (2013) Implementation of a hospital oral care protocol and recording of oral mucositis in children receiving cancer treatment : a retrospective and a prospective study. Support Care Cancer 21(4):1113–1120
24. Martinez JM, Pereira D, Chacim S, Mesquita E, Sousa I, Martins Â, Azevedo T, Mariz JM (2014) Mucositis care in acute leukemia and non-Hodgkin lymphoma patients undergoing high-dose chemotherapy. Support Care Cancer 22(9):2563–2569
25. Soares AF, Aquino ARL, Carvalho CHP, Nonaka CFW, Almeida D, Pinto LP (2011) Frequency of oral mucositis and microbiological analysis in children with acute lymphoblastic leukemia treated with 0.12% chlorhexidine gluconate. Braz Dent J 22(4):312–316

26. Mason H, DeRubeis MB, Foster JC, Taylor JMG, Worden FP (2013) Outcomes evaluation of a weekly nurse practitioner-managed symptom management clinic for patients with head and neck cancer treated with chemoradiotherapy. Oncol Nurs Forum 40(6):581–586
27. Salvador P, Azusano C, Wang L, Howell D (2012) A pilot randomized controlled trial of an oral care intervention to reduce mucositis severity in stem cell transplant patients. J Pain Symptom Manag 44(1):64–73
28. Soga Y, Sugiura Y, Takahashi K, Nishimoto H, Maeda Y, Tanimoto M, Takashiba S (2010) Progress of oral care and reduction of oral mucositis–a pilot study in a hematopoietic stem cell transplantation ward. Support Care Cancer 19(2):303–307
29. Saito H, Watanabe Y, Sato K, Ikawa H, Yoshida Y, Katakura A, Takayama S, Sato M (2014) Effects of professional oral health care on reducing the risk of chemotherapy-induced oral mucositis. Support Care Cancer 22(11):2935–2940
30. Kartin PT, Tasci S, Soyuer S, Elmali F (2014) Effect of an oral mucositis protocol on quality of life of patients with head and neck cancer treated with radiation therapy. Clin J Oncol Nurs 18(6): E118–E125
31. Leppla L, de Geest S, Fierz K, Deschler-Baier B, Koller A (2016) An oral care self-management support protocol (OrCaSS) to reduce oral mucositis in hospitalized patients with acute myeloid leukemia and allogeneic hematopoietic stem cell transplantation: a randomized controlled pilot study. Support Care Cancer 24(2):773–782
32. Diaz-Sanchez RM, Pachón-Ibáñez J, Marín-Conde F, Rodríguez-Caballero Á, Gutierrez-Perez JL, Torres-Lagares D (2015) Double-blind, randomized pilot study of bioadhesive chlorhexidine gel in the prevention and treatment of mucositis induced by chemoradiotherapy of head and neck cancer. Med Oral Patol Oral Cir Bucal 20(3):e378–e385
33. Choi SE, Kim HS (2012) Sodium bicarbonate solution versus chlorhexidine mouthwash in oral care of acute leukemia patients undergoing induction chemotherapy: a randomized controlled trial. Asian Nurs Res (Korean Soc Nurs Sci) 6(2):60–66
34. Mehdipour M, Taghavi Zenoz A, Asvadi Kermani I, Hosseinpour A (2011) A comparison between zinc sulfate and chlorhexidine gluconate mouthwashes in the prevention of chemotherapy-induced oral mucositis. Daru 19(1):71–73
35. Mutters NT, Neubert TR, Nieth R, Mutters R (2015) The role of Octenidol((R)), Glandomed((R)) and chlorhexidine mouthwash in the prevention of mucositis and in the reduction of the oropharyngeal flora: a double-blind randomized controlled trial. GMS Hyg Infect Control 10:Doc05
36. Roopashri G, Jayanthi K, Guruprasad R (2011) Efficacy of benzydamine hydrochloride, chlorhexidine, and povidone iodine in the treatment of oral mucositis among patients undergoing radiotherapy in head and neck malignancies: a drug trail. Contemp Clin Dent 2(1):8–12
37. Djuric M, Hillier-Kolarov V, Belic A, Jankovic L (2006) Mucositis prevention by improved dental care in acute leukemia patients. Support Care Cancer 14(2):137–146
38. Yoneda S, Imai S, Hanada N, Yamazaki T, Senpuku H, Ota Y, Uematsu H (2007) Effects of oral care on development of oral mucositis and microorganisms in patients with esophageal cancer. Jpn J Infect Dis 60(1):23–28
39. Kubota K, Kobayashi W, Sakaki H, Nakagawa H, Kon T, Mimura M, Ito R, Furudate K, Kimura H (2015) Professional oral health care reduces oral mucositis pain in patients treated by superselective intra-arterial chemotherapy concurrent with radiotherapy for oral cancer. Support Care Cancer 23(11):3323–3329
40. Yokota T, Tachibana H, Konishi T, Yurikusa T, Hamauchi S, Sakai K, Nishikawa M, Suzuki M, Naganawa Y, Hagihara T, Tsumaki H, Kubo T, Sato M, Taguri M, Morita S, Eguchi T, Kubota K, Zenda S (2016) Multicenter phase II study of an oral care program for patients with head and neck cancer receiving chemoradiotherapy. Support Care Cancer 24(7):3029–3036
41. Melkos AB, Massenkeil G, Arnold R, Reichart PA (2003) Dental treatment prior to stem cell transplantation and its influence on the posttransplantation outcome. Clin Oral Investig 7(2):113–115
42. Santos PS, Coracin FL, Barros JC, Dulley FL, Nunes FD, Magalhães MG (2011) Impact of oral care prior to HSCT on the severity and clinical outcomes of oral mucositis. Clin Transpl 25(2):325–328
43. Kashiwazaki H, Matsushita T, Sugita J, Shigematsu A, Kasashi K, Yamazaki Y, Kanehira T, Yamamoto S, Kondo T, Endo T, Tanaka J, Hashino S, Nishio M, Imamura M, Kitagawa Y, Inoue N (2012) Professional oral health care reduces oral mucositis and febrile neutropenia in patients treated with allogeneic bone marrow transplantation. Support Care Cancer 20(2):367–373
44. Gurgan CA, Özcan M, Karakus Ö, Zincircioglu G, Arat M, Soydan E, Topcuoglu P, Gürman G, Bostanci HS (2013) Periodontal status and post-transplantation complications following intensive periodontal treatment in patients underwent allogenic hematopoietic stem cell transplantation conditioned with myeloablative regimen. Int J Dent Hyg 11(2):84–90
45. Rojas de Morales T, Zambrano O, Rivera L, Navas R, Chaparro N, Bernardonni C, Rivera F, Fonseca N, Tirado DM (2001) Oral-disease prevention in children with cancer: testing preventive protocol effectiveness. Med Oral 6(5):326–334
46. Levy-Polack MP, Sebelli P, Polack NL (1998) Incidence of oral complications and application of a preventive protocol in children with acute leukemia. Spec Care Dentist 18(5):189–193
47. Cheng KK, Molassiotis A, Chang AM, Wai WC, Cheung SS (2001) Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in paediatric cancer patients. Eur J Cancer 37(16):2056–2063
48. Cheng KK, Molassiotis A, Chang AM (2002) An oral care protocol intervention to prevent chemotherapy-induced oral mucositis in paediatric cancer patients: a pilot study. Eur J Oncol Nurs 6(2):66–73
49. Chen CF, Wang RH, Cheng SN, Chang YC (2004) Assessment of chemotherapy-induced oral complications in children with cancer. J Pediatr Oncol Nurs 21(1):33–39
50. Kenny SA (1990) Effect of two oral care protocols on the incidence of stomatitis in hematology patients. Cancer Nurs 13(6):345-53
51. Shieh SH, Wang ST, Tsai ST, Tseng CC (1997) Mouth care for nasopharyngeal cancer patients undergoing radiotherapy. Oral Oncol 33(1):36–41
52. Janjan NA, Weissman DE, and Pahule A (1992) Improved pain management with daily nursing intervention during radiation therapy for head and neck carcinoma. Int J Radiat Oncol Biol Phys 23(3):647–652
53. Yuce UO, Yurtsever S (2017) Effect of education about oral mucositis given to the cancer patients having chemotherapy on life quality. J Cancer Educ
54. Borowski B, Benhamou E, Pico JL, Laplanche A, Margainaud JP, Hayat M (1994) Prevention of oral mucositis in patients treated with high-dose chemotherapy and bone marrow transplantation: a randomised controlled trial comparing two protocols of dental care. Eur J Cancer B Oral Oncol 30B(2):93–97
55. Bhatt V, Vendrell N, Nau K, Crumb D, Roy V (2010) Implementation of a standardized protocol for prevention and management of oral mucositis in patients undergoing hematopoietic cell transplantation. J Oncol Pharm Pract 16(3):195–204
56. Yamagata K, Arai C, Sasaki H, Takeuchi Y, Onizawa K, Yanagawa T, Ishibashi N, Karube R, Shinozuka K, Hasegawa Y, Chiba S, Bukawa H (2012) The effect of oral management on the severity of oral mucositis during hematopoietic SCT. Bone Marrow Transplant 47(5):725–730
57. Legert KG, Remberger M, Ringdén O, Heimdahl A, Dahllöf G (2014) Reduced intensity conditioning and oral care measures

prevent oral mucositis and reduces days of hospitalization in allogeneic stem cell transplantation recipients. Support Care Cancer 22(8):2133–2140
58. Schmidt H, Boese S, Bauer A, Landenberger M, Lau A, Stoll O, Schmoll HJ, Mauz-Koerholz C, Kuss O, Jahn P (2017) Interdisciplinary care programme to improve self-management for cancer patients undergoing stem cell transplantation: a prospective non-randomised intervention study. Eur J Cancer Care (Engl) 26(4)
59. Yavuz B, Bal Yilmaz H (2015) Investigation of the effects of planned mouth care education on the degree of oral mucositis in pediatric oncology patients. J Pediatr Oncol Nurs 32(1):47–56
60. Feber T (1996) Management of mucositis in oral irradiation. Clin Oncol (R Coll Radiol) 8(2):106–111
61. Vokurka S, Bystřická E, Koza V, Sčudlová J, Pavlicová V, Valentová D, Bocková J, Mišaniová L (2005) The comparative effects of povidone-iodine and normal saline mouthwashes on oral mucositis in patients after high-dose chemotherapy and APBSCT–results of a randomized multicentre study. Support Care Cancer 13(7):554–558
62. Dudjak LA (1987) Mouth care for mucositis due to radiation therapy. Cancer Nurs 10(3):131–140
63. McGaw WT, Belch A (1985) Oral complications of acute leukemia: prophylactic impact of a chlorhexidine mouth rinse regimen. Oral Surg Oral Med Oral Pathol 60(3):275–280
64. Ferretti GA, Raybould TP, Brown AT, Macdonald JS, Greenwood M, Maruyama Y, Geil J, Lillich TT, Ash RC (1990) Chlorhexidine prophylaxis for chemotherapy- and radiotherapy-induced stomatitis: a randomized double-blind trial. Oral Surg Oral Med Oral Pathol 69(3):331–338
65. Rutkauskas JS, Davis JW (1993) Effects of chlorhexidine during immunosuppressive chemotherapy. A preliminary report. Oral Surg Oral Med Oral Pathol 76(4):441–448
66. Dodd MJ, Larson PJ, Dibble SL, Miaskowski C, Greenspan D, MacPhail L, Hauck WW, Paul SM, Ignoffo R, Shiba G (1996) Randomized clinical trial of chlorhexidine versus placebo for prevention of oral mucositis in patients receiving chemotherapy. Oncol Nurs Forum 23(6):921–927
67. Sorensen JB, Skovsgaard T, Bork E, Damstrup L, Ingeberg S (2008) Double-blind, placebo-controlled, randomized study of chlorhexidine prophylaxis for 5-fluorouracil-based chemotherapy-induced oral mucositis with nonblinded randomized comparison to oral cooling (cryotherapy) in gastrointestinal malignancies. Cancer 112(7):1600–1606
68. Spijkervet FK, van Saene HK, Panders AK, Vermey A, van Saene JJ, Mehta DM, Fidler V (1989) Effect of chlorhexidine rinsing on the oropharyngeal ecology in patients with head and neck cancer who have irradiation mucositis. Oral Surg Oral Med Oral Pathol 67(2):154–161
69. Foote RL, Loprinzi CL, Frank AR, O'Fallon JR, Gulavita S, Tewfik HH, Ryan MA, Earle JM, Novotny P (1994) Randomized trial of a chlorhexidine mouthwash for alleviation of radiation-induced mucositis. J Clin Oncol 12(12):2630–2633
70. Ferretti GA, Ash RC, Brown AT, Parr MD, Romond EH, Lillich TT (1988) Control of oral mucositis and candidiasis in marrow transplantation: a prospective, double-blind trial of chlorhexidine digluconate oral rinse. Bone Marrow Transplant 3(5):483–493
71. Raether D, Walker PO, Bostrum B, Weisdorf D (1989) Effectiveness of oral chlorhexidine for reducing stomatitis in a pediatric bone marrow transplant population. Pediatr Dent 11(1):37–42
72. Weisdorf DJ, Bostrom B, Raether D, Mattingly M, Walker P, Pihlstrom B, Ferrieri P, Haake R, Goldman A, Woods W, et al. (1989) Oropharyngeal mucositis complicating bone marrow transplantation: prognostic factors and the effect of chlorhexidine mouth rinse. Bone Marrow Transplant 4(1): 89–95
73. Pitten FA, Kiefer T, Buth C, Doelken G, Kramer A (2003) Do cancer patients with chemotherapy-induced leukopenia benefit from an antiseptic chlorhexidine-based oral rinse? A double-blind, block-randomized, controlled study. J Hosp Infect 53(4):283–291
74. Cheng KK, Chang AM, Yuen MP (2004) Prevention of oral mucositis in paediatric patients treated with chemotherapy; a randomised crossover trial comparing two protocols of oral care. Eur J Cancer 40(8):1208–1216
75. Dodd MJ, Dibble SL, Miaskowski C, MacPhail L, Greenspan D, Paul SM, Shiba G, Larson P (2000) Randomized clinical trial of the effectiveness of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90(1):39–47
76. Samaranayake LP, Robertson AG, MacFarlane TW, Hunter IP, MacFarlane G, Soutar DS, Ferguson MM (1988) The effect of chlorhexidine and benzydamine mouthwashes on mucositis induced by therapeutic irradiation. Clin Radiol 39(3):291–294
77. Kin-Fong Cheng K, Ka Tsui Yuen J (2006) A pilot study of chlorhexidine and benzydamine oral rinses for the prevention and treatment of irradiation mucositis in patients with head and neck cancer. Cancer Nurs 29(5):423–430
78. Madan PD, Sequeira PS, Shenoy K, Shetty J (2008) The effect of three mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies: a randomized control trial. J Cancer Res Ther 4(1):3–8
79. Epstein JB, Vickars L, Spinelli J, Reece D (1992) Efficacy of chlorhexidine and nystatin rinses in prevention of oral complications in leukemia and bone marrow transplantation. Oral Surg Oral Med Oral Pathol 73(6):682–689
80. Dodd MJ, Miaskowski C, Greenspan D, MacPhail L, Shih AS, Shiba G, Facione N, Paul SM (2003) Radiation-induced mucositis: a randomized clinical trial of micronized sucralfate versus salt & soda mouthwashes. Cancer Investig 21(1):21–33
81. Seto BG, Kim M, Wolinsky L, Mito RS, Champlin R (1985) Oral mucositis in patients undergoing bone marrow transplantation. Oral Surg Oral Med Oral Pathol 60(5):493–497
82. Lindquist SF, Hickey AJ, Drane JB (1978) Effect of oral hygiene on stomatitis in patients receiving cancer chemotherapy. J Prosthet Dent 40(3):312–314
83. Antunes HS, Ferreira EM, de Faria LM, Schirmer M, Rodrigues PC, Small IA, Colares M, Bouzas LF, Ferreira CG (2010) Streptococcal bacteraemia in patients submitted to hematopoietic stem cell transplantation: the role of tooth brushing and use of chlorhexidine. Med Oral Patol Oral Cir Bucal 15(2):e303–e309
84. Elad S, Raber-Durlacher JE, Brennan MT, Saunders DP, Mank AP, Zadik Y, Quinn B, Epstein JB, Blijlevens NM, Waltimo T, Passweg JR, Correa ME, Dahllöf G, Garming-Legert KU, Logan RM, Potting CM, Shapira MY, Soga Y, Stringer J, Stokman MA, Vokurka S, Wallhult E, Yarom N, Jensen SB (2015) Basic oral care for hematology-oncology patients and hematopoietic stem cell transplantation recipients: a position paper from the joint task force of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and the European Society for Blood and Marrow Transplantation (EBMT). Support Care Cancer 23(1):223–236
85. Costa EM, et al. (2003) Evaluation of an oral preventive protocol in children with acute lymphoblastic leukemia. Pesqui Odontol Bras 17(2):147–50

86. Cabrera-Jaime S, Martínez C, Ferro-García T, Giner-Boya P, Icart-Isern T, Estrada-Masllorens JM, Fernández-Ortega P (2018) Efficacy of Plantago major, chlorhexidine 0.12% and sodium bicarbonate 5% solution in the treatment of oral mucositis in cancer patients with solid tumour: a feasibility randomised triple-blind phase III clinical trial. Eur J Oncol Nurs 32:40–47
87. Huang BS, Wu SC, Lin CY, Fan KH, Chang JTC, Chen SC (2018) The effectiveness of a saline mouth rinse regimen and education programme on radiation-induced oral mucositis and quality of life in oral cavity cancer patients: a randomised controlled trial. Eur J Cancer Care (Engl) 27(2):e12819