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SPECIAL ARTICLE

Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients and clinical practice guidelines

Deborah P. Saunders[1] · Tanya Rouleau[1] · Karis Cheng[2] · Noam Yarom[3] · Abhishek Kandwal[4] · Jamie Joy[5] · Kivanc Bektas Kayhan[6] · Marianne van de Wetering[7] · Norman Brito-Dellan[8] · Tomoko Kataoka[9] · Karen Chiang[10] · Vinisha Ranna[11] · Anusha Vaddi[12] · Joel Epstein[13] · Rajesh V. Lalla[14] · Paolo Bossi[15] · Sharon Elad[12] · On behalf of the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO)

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Abstract

Purpose To update the clinical practice guidelines for the use of antimicrobials, mucosal coating agents, anesthetics, and analgesics 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 of 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 2014 MASCC/ISOO clinical practice guidelines. Based on the evidence level, the following guidelines were determined: Recommendation, Suggestion, and No Guideline Possible.

Results A total of 9 new papers were identified within the scope of this section, adding to the 62 papers reviewed in this section previously. A new Suggestion was made for topical 0.2% morphine for the treatment of OM-associated pain in head and neck (H&N) cancer patients treated with RT-CT (modification of previous guideline). A previous Recommendation against the use of sucralfate-combined systemic and topical formulation in the prevention of OM in solid cancer treatment with CT was changed from Recommendation Against to No Guideline Possible. Suggestion for doxepin and fentanyl for the treatment of mucositis-associated pain in H&N cancer patients was changed to No Guideline Possible.

✉ Deborah P. Saunders
dsaunders@hsnsudbury.ca

[1] Dental Oncology Program, Health Sciences North, North East Cancer Center, Northern Ontario School of Medicine, 41 Ramsey Lake Road, Sudbury, Ontario P3E 5J1, Canada

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

[3] Oral Medicine Unit, Sheba Medical Center, Tel Hashomer, Israel and School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel

[4] Cancer Research Institute, Himalayan Institute of Medical Sciences, Swami Rama Himayalan University, Dehradun, Uttarakhand, India

[5] Clinical Pharmacy, Cancer Treatment Centers of America, Boca Raton, FL, USA

[6] Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, İstanbul University, Istanbul, Turkey

[7] Paediatric Oncology Department, Emma Children's Hospital, Academic Medical Centre, Amsterdam, The Netherlands

[8] Division of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[9] Multi-institutional Clinical Trials Section, Research Management Division, Clinical Research Support Office, National Cancer Center Hospital, Tokyo, Japan

[10] Pharmacy Department, St Vincent's Hospital Melbourne, Electronic Medical Records Department, Melbourne Health, Jane Bell House, Melbourne, Victoria, Australia

[11] Department of Oral and Maxillofacial Surgery, The Mount Sinai Hospital, New York, NY, USA

[12] Oral Medicine, Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY, USA

[13] Cedars-Sinai Health System, Los Angeles CA and City of Hope National Medical Center, Duarte, CA, USA

[14] Section of Oral Medicine, University of Connecticut School of Dental Medicine, Farmington, CT, USA

[15] Medical Oncology, University of Brescia, ASST-Spedali Civili, Brescia, Italy

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Conclusions Of the agents studied for the management of OM in this paper, the evidence supports a Suggestion in favor of topical morphine 0.2% in H&N cancer patients treated with RT-CT for the treatment of OM-associated pain.

Keywords Antimicrobials · Mucosal coating agents · Anesthetics · Analgesics · Oral mucositis

Introduction

Oral mucositis (OM) is a highly significant and potentially dose-limiting complication of cancer therapy. The morbidity of OM is primarily due to pain associated with the oral mucosal inflammation and ulceration [1]. OM pain negatively affects oral intake including dietary intake and oral medications, maintenance of oral hygiene, and quality of life [2]. Therefore, there has been significant interest in the use of agents that can alleviate OM-associated pain. Such agents may be topical anesthetics or analgesics. Additionally, topical coating agents may protect the oral mucosa, facilitate healing, and cover exposed nerve endings. Another concern with OM relates to colonization of the oral ulcerations by microbial flora. While OM is not of infectious etiology, secondary microbial colonization of oral lesions can cause clinically relevant local or systemic infection and can theoretically exacerbate OM severity.

While there is a growing body of literature on these agents, the results are frequently conflicting. To support evidence-based patient management and improve clinical outcomes, the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has published evidence-based clinical practice guidelines for mucositis [3, 4]. This set of guidelines included a section devoted for antimicrobial, mucosal coating, anesthetic, and analgesic agents [5].

In the previous guideline update, a Recommendation was developed in favor of patient-controlled analgesia with morphine in hematopoietic stem cell transplant (HSCT) patients. Suggestions were developed in favor of transdermal fentanyl in standard-dose chemotherapy and HSCT patients and morphine mouth rinse and doxepin rinse in head and neck (H&N) radiation therapy (RT) patients. Recommendations were developed against the use of topical antimicrobial agents for prevention of OM. These included recommendations against the use of iseganan for OM prevention in HSCT and H&N RT and against the use of antimicrobial lozenges (polymyxin-tobramycin-amphotericin B lozenges/paste and bacitracin-clotrimazole-gentamicin lozenges) for OM prevention in H&N RT. Recommendations were developed against the use of the mucosal coating agent sucralfate for the prevention or treatment of chemotherapy (CT) or RT-induced OM. No guidelines were possible for any other agent due to insufficient and/or conflicting evidence.

As part of a comprehensive update of the MASCC/ISOO clinical practice guidelines for mucositis, the aim of this project was to update the evidence-based clinical practice guidelines for the use of antimicrobials, mucosal coating agents, anesthetics, and analgesic agents for the prevention and treatment of OM.

Methods

The methods are described in detail in Ranna et al. (2019) [6]. Briefly, a search for relevant papers indexed in the literature from 1 Jan. 2011 to 30 June 2016 was conducted using PubMed/Web of Science/EMBASE, with papers selected for review based on defined inclusion and exclusion criteria.

Papers were reviewed by two independent reviewers and data were extracted using a standard electronic form. Studies were scored for their level of evidence (LoE) based on Somerfield criteria [7], and flaws were listed according to Hadorn criteria [8]. A well-designed study was defined as a study with no major flaws per the Hadorn criteria.

Findings from the reviewed studies were merged with the evidence reviewed in the previous MASCC/ISOO guideline update. Then, findings from the reviewed studies were integrated into guidelines based on the overall LoE for each intervention. Guidelines were classified into 3 types: Recommendation, Suggestion, and No Guideline Possible.

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

The list of intervention keywords used for the literature search of this section is presented in the Ranna et al. (2019) Methods paper [6].

Results

The literature search identified 1552 papers: 665 from PubMed and 887 from Web of Science. Additional 10 papers were identified based on a manual check of reference lists. After careful assessment of the abstracts, 1555 articles were excluded due to repetition across databases, non-clinical studies, meta-analyses, and reviews. Seven articles underwent the final review and were merged with the 62 papers that were reviewed in the 2013 guideline update in this section. A total of 69 papers were included in this report.

Antifungals

Candidiasis is a common superficial oral infection in cancer patients, which can complicate OM as a secondary infection and aggravate the symptoms. Furthermore, colonization of candidal hyphae within the oral mucosa may delay OM healing. Therefore, it was hypothesized that antifungals may prevent OM.

Fluconazole (systemic)—H&N—RT/RT-CT—prevention

Miconazole (topical and systemic)—hematologic cancer—HSCT—prevention

Guideline: No Guideline Possible

Two new publications were directed to use of antifungal agents for prevention of OM (Table 1) [11, 12]. These papers did not provide sufficient evidence to upgrade the guidelines. Interestingly, a new antifungal with a novel formulation was introduced: miconazole delivered as a mucoadhesive buccal tablet [12]. This formula is expected to have a sustained topical affect while the tablet is dissolving, as well as a systemic effect when the agent is swallowed and absorbed. This study did not report on OM, rather indirect indicators (duration of hospitalization, morphine use) for OM.

Coating agents

Considering that cancer therapy makes the oral mucosa more sensitive to physiological trauma, coating agents are designed to form a barrier that reduces irritation. A variety of agents have been suggested. During this systematic review, we found reports about a new proprietary viscous liquid mucoadhesive hydrogel (MAH) [13].

MAH (topical)—H&N cancer—RT-CT—treatment

Guideline: No Guideline Possible

A RCT compared a proprietary MAH to sham in H&N cancer patients for the treatment of OM (Table 2) [13]. The agent effectively mitigated OM symptoms as reflected by the area under the curve of daily patient-reported oral soreness and WHO scores on the last day of radiation therapy. Both parameters reflect relief in symptoms. As there was only one publication for this agent, it was impossible to form a guideline.

Polyvinylpyrrolidone (topical)—H&N cancer—RT-CT—treatment

Polyvinylpyrrolidone (topical)—H&N cancer—RT—treatment

Polyvinylpyrrolidone (topical)—hematologic patients—HSCT—treatment

Guideline: No Guideline Possible

The studies reviewed for this agent are categorized according to the clinical setting (Table 2) [14–16]. There was insufficient evidence to form a guideline.

Sucralfate

Sucralfate is a compound of sucrose sulfate and aluminum hydroxide that presumably acts as a coating agent, protecting the mucosal surface from irritants during healing [17]. Additionally, sucralfate stimulates prostaglandin release, increases mucus production and viscosity, activates mucosal macrophages, increases prostaglandin-dependent cell proliferation and mucosal blood flow–stimulated angiogenesis, and promotes granulation tissue formation [18, 19]. Although many of these findings were reported in the GI mucosa, they may also contribute to oral mucosal protection.

Sucralfate (combined topical and systemic administration): H&N cancer—RT—prevention

Guideline: Recommendation, against (LoE II)

Sucralfate is not recommended for the prevention of OM-associated pain in H&N cancer patients treated with RT.

The efficacy of sucralfate administration for the prevention of OM in H&N cancer patients receiving RT was examined in 5 RCTs including 4 RCTs with no major flaws (Table 3). Of these, 4 reported that sucralfate was not effective for the prevention of OM [26–29] and one reported that sucralfate was effective [23]. The sucralfate preparation varied in consistency and mode of administration. In 3 RCTs, an oral suspension of

Table 1 Studies reported for antifungals, overall level of evidence, and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author (year)	Effective	Overall level of evidence	Guideline category	Non-RCT studies
Fluconazole	Systemic	H&N	RT/RT-CT	P	Corvo (2008) [9]	N	III	NGP	Nicolatou-Galitis (2006) [10]—3 (Y), Rao (2013) [11]—4 (Y)
Miconazole	Topical and systemic	Hematol	HSCT	P			III	NGP	Orvain (2015) [12]—3 (Y)

Non-RCT studies keys: [3] non-RCT, [4] cohort, [5] before and after, [6] case-control studies, [7] cross-sectional, [8] case series, [11] case report, [12] expert opinion

NGP no guideline possible; *HSCT* hematopoietic stem cell transplant; *H&N* head and neck; *RT* radiotherapy; *CT* chemotherapy; *Hematol* hematological; *ca.* cancer; *PO* per os; *P* prevention; *Y* yes, effective; *N* no, ineffective

Table 2 Studies reported for coating agents, overall level of evidence, and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author (year)	Effective	Overall level of evidence	Guideline category	Non-RCT studies
Mucoadhesive hydrogel (MuGuard)	Mouthwash	H&N	RT-CT	T	Allison (2014) [13]	Y [2, 3]	II	NGP	
Polyvinylpyrrolidone	Mouthwash	H&N	RT-CT	T	Barber (2007) [14]	N	III	NGP	
	Mouthwash	H&N	RT	T			IV	NGP	Lindsay (2009) [15]—5 (Y)
	Mouthwash	Hematol	HSCT	T	-	-	IV	NGP	Vokurka (2011) [16]—6 (N)

Non-RCT studies keys: [3] non-RCT, [4] cohort, [5] before and after, [6] case-control studies, [7] cross-sectional, [8] case series, [11] case report, [12] expert opinion

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sucralfate was given as a swish-and-swallow mouthwash [26, 27, 29], in one RCT, it was applied as a unique formula of mouthwash and a gel [28], and in another, it was unclear whether the oral suspension was swallowed or not [23]. In most RCTs, sucralfate did not reduce the severity of OM or relieve OM-associated pain. All studies included RT patients only, and in a single RCT that studied a mixed patient population, ~75% of patients were treated with RT only and ~25% of patients were treated with RT-CT [29].

Two other comparative studies showed opposing results (Table 1) [24, 25]. No new studies were published in this category since the previous guideline update [5].

A RCT comparing GM-CSF with sucralfate concluded that GM-CSF mouthwash may be moderately more effective than sucralfate mouthwash in preventing RT-induced OM and OM-related pains [40]. Since this comparator study used an active control, it cannot be integrated with RCTs comparing sucralfate with a sham treatment.

Sucralfate (topical): H&N cancer—RT—treatment

Guideline: Recommendation (LoE III)

Sucralfate is not recommended for the treatment of OM-associated pain in H&N cancer patients treated with RT.

Two RCTs assessed sucralfate as a treatment for OM-associated pain in patients treated with RT for H&N cancer [33, 35]. Both studies concluded that sucralfate was not effective for this goal. These RCTs differed in the mode of application: topical combined with systemic administration [33] vs. topical only [35]. A comparative study pointed at the same trend [34].

Sucralfate (combined topical and systemic): H&N cancer—CT—prevention

Guideline: No Guideline Possible

A single RCT with H&N cancer patients was designed as a cross-over study (Table 3) [30], where one group was randomized for sucralfate in the first CT cycle and the second group was assigned a placebo in the first CT cycle. This study reported that sucralfate did not reduce OM severity. Ten of the 23 study patients discontinued the study, seven due to nausea.

Sucralfate (combined topical and systemic): solid cancer—CT—Treatment

Guideline: Recommendation, against (LoE II)

Sucralfate is not recommended for the treatment of OM-associated pain in solid cancer patients treated with CT.

Two well-designed RCTs reported that sucralfate used as a swish-and-swallow oral suspension was ineffective for the treatment of OM in patients with solid tumors (Table 3) [38, 39]. There was no new evidence in this category, and therefore, the guideline remains unchanged.

Analgesics

Morphine

The rationale for topical morphine application is that opioid receptors on the peripheral terminals of primary afferent nerves can mediate potent antinociceptive effects [41]. Inhibition of neuronal excitability of peripheral nociceptors may reduce the need for systemic opioids, thereby diminishing central side effects.

Morphine (topical): H&N cancer—RT-CT—treatment

Guideline: Suggestion (LoE III)

Topical morphine 0.2% mouthwash is suggested for the treatment of OM-associated pain in H&N cancer patients treated with RT-CT.

Topical morphine at 0.2% concentration was reported in 2 RCTs for the treatment of OM-associated pain in patients with H&N cancer treated with RT-CT or RT only (Table 4). The earlier study compared 0.2% morphine swish-and-spit with "magic mouthwash," which includes equal parts of lidocaine, diphenhydramine, and

Table 3 Studies reported for sucralfate, overall level of evidence, and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author (year)	Effective	Overall level of evidence	Guideline category	Guideline determination	Non-RCT studies
Sucralfate	Topical and systemic	Solid cancer	CT	P	Ala (2016) [20]	Y [1–3]	I	NGP		
					Nottage (2003) [21]	N				
	Topical and systemic	Hematol	CT	P	Shenep (1988) [22]	N	III	NGP		
	Topical and systemic	H&N	RT	P	Etiz (2000) [23]	Y [1]	II	Recommendation (against)	Sucralfate is not recommended for the prevention of OM-associated pain in H&N cancer patients treated with RT	Cengiz (1999) [24]—3 (Y), Matthews (1996) [25]—3 (N)
					Epstein (1994) [26]	N				
					Makkonen (1994) [27]	N				
					Evenson (2001) [28]	N				
	Topical and systemic	H&N	RT-CT	P	Carter (1999) [29]*	N				
	Topical and systemic	H&N	CT	P	Pfeiffer (1990) [30]	Y [1]	III	NGP		
	Topical	H&N/solid cancer	RT	P				NGP		Giorgi (1996) [31]—5 (Y)
	Topical and systemic	Hematol	HSCT	P	Castagna (2001) [32]	N	III	NGP		
	Topical and systemic	H&N	RT	T	Lievens (1998) [33]	N	II	Recommendation (against)	Sucralfate is not recommended for the treatment of OM-associated pain in H&N cancer patients treated with RT	Barker (1991) [34]—3 (N)
					Meredith (1997) [35]	N				
	Topical	H&N	RT or RT/CT	T	Dodd (2003) [36]	N	III	NGP		
	Topical	H&N	RT	T	Franzen (1995) [37]	Y [1]**	III	NGP		
	Topical and systemic	Solid cancer	CT	T	Chiara (2001) [38]	N	II	Recommendation	Sucralfate is not recommended for the treatment of OM-associated pain in solid cancer patients treated with CT	
					Loprinzi (1997) [39]	N				

Non-RCT studies keys: [3] non-RCT, [4] cohort, [5] before and after, [6] case-control studies, [7] cross-sectional, [8] case series, [11] case report, [12] expert opinion

NGP no guideline possible; *HSCT* hematopoietic stem cell transplant; *H&N* head and neck; *RT* radiotherapy; *CT* chemotherapy; *Hematol* hematological; ca. cancer; *PO* per os; *P* prevention; *Y* yes, effective; *N* no, ineffective

*Most of the patients in this study were treated with RT only

**Significant reduction of OM severity during the first 3 weeks of intervention, which coincided with the first 5 weeks of RT, i.e., correlating with moderate dose of RT

magnesium aluminum hydroxide [42]. All the patients in this RCT underwent RT-CT. This study showed that the severity and duration of OM were less in the morphine group. Another RCT used a mixed group of patients in a cross-over study, where the groups were switched after 3 days of treatment [44]. The morphine was applied as a 0.2% swish-and-spit solution, and the placebo group received quinine diHCl at 50 mg/15 mL to mimic the bitter taste of morphine. This study had a small sample size of 9 patients, 8 out of them had H&N cancer, and 7 out of the H&N were treated with RT-CT. This study concluded that topical morphine reduced the severity of OM. A third RCT in H&N cancer patients administered a 2% dose of topical morphine and compared it with "magic mouthwash" composed of magnesium aluminum hydroxide-viscous lidocaine-diphenhydramine [45]. This study reported that 2% morphine was effective in reducing the severity of OM. This RCT was heterogeneous with regard to cancer therapy, which possibly confounded the results. Although all RCTs had a small sample size and used different placebos, the consistency of the results facilitated a Suggestion in favor of topical morphine 0.2%.

Several studies were published in other categories (Table 4) [36, 37]. However, the evidence was too weak to reach a guideline in favor of morphine treatment for OM-associated pain.

Doxepin

Doxepin is a tricyclic antidepressant, which is prescribed for various indications such as insomnia, depression, anxiety, and urticaria. Doxepin blocks the neuronal reuptake of serotonin (5-HT) and norepinephrine (NE) [48, 49]. Likewise, doxepin blocks alpha-adrenergic receptors, as well as sodium ion channels [48]. These pathways may interfere with transmission of the pain impulse. Additionally, doxepin is a powerful antihistamine and it binds to the H1 receptor and antagonizes its action [38, 40].

Doxepin (topical)—H&N cancer patients—RT—treatment Guideline: No Guideline Possible

A single RCT in patients with H&N cancer was published comparing doxepin 0.5% mouthwash to placebo (Table 5) [50]. This study reported pain reduction following its application. Doxepin was associated with more stinging or burning, unpleasant taste, and greater drowsiness than the placebo rinse. Additional studies in mixed cancer patient population were published earlier [42, 43]; however, there was insufficient evidence to support a guideline for this agent.

Fentanyl

Fentanyl—H&N cancer patients—RT or RT-CT—treatment

Fentanyl—Hematologic cancer patients—HSCT—treatment

Table 4 Studies reported for morphine, overall level of evidence, and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author (year)	Effective	Overall level of evidence	Guideline category	Guideline determination	Non-RCT studies
Morphine	Topical	H&N	RT-CT	T	Cercheitti (2002) [42]* (0.2%)	Y [3, 4]	III	Suggestion	Morphine 0.2% mouthwash is not suggested for the treatment of OM-associated pain in H&N cancer patients treated with RT-CT	Cerchetti (2003) [43]—4 (Y)
	Topical	Solid and Hematol	CT/RT or RT-CT to H&N	T	Vayne-Bossert (2010) [44] (0.2%)	Y [1]				
	Topical	H&N	RT/RT-CT/CT	T	Sarvizadeh (2015) [45] (2%)	Y [1]				
	Topical	Solid	CT	T						Krajnik (1999) [46]—8 (Y)
	G-tube	H&N	RT/RT-CT	T						Shaiova (2007) [47]—7 (Y)

Non-RCT studies keys: [3] non-RCT, [4] cohort, [5] before and after, [6] case-control studies, [7] cross-sectional, [8] case series, [11] case report, [12] expert opinion

NGP no guideline possible; *HSCT* hematopoietic stem cell transplant; *H&N* head and neck; *RT* radiotherapy; *CT* chemotherapy; *Hematol* hematological; ca. cancer; *PO* per os; *P* prevention; *Y* yes, effective; *N* no, ineffective

*Compared with magic mouthwash—lidocaine, diphenhydramine, and magnesium aluminum hydroxide

Table 5 Studies reported for doxepin, overall level of evidence, and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author (year)	Effective	Overall level of evidence	Guideline category	Non-RCT studies
Doxepin	Mouthwash	H&N	RT or RT-CT	T	Leenstra (2014) [50]	Y [3]	II	NGP	
		H&N cancer and Hematol	RT or RT-CT or CT	T			III	NGP	Epstein (2001) [51]—5 (Y), Epstein (2008) [52]—5 (Y)

Non-RCT studies keys: [3] non-RCT, [4] cohort, [5] before and after, [6] case-control studies, [7] cross-sectional, [8] case series, [11] case report, [12] expert opinion

NGP no guideline possible; *HSCT* hematopoietic stem cell transplant; *H&N* head and neck; *RT* radiotherapy; *CT* chemotherapy; *Hematol* hematological; *ca*. cancer; *PO* per os; *P* prevention; *Y* yes, effective; *N* no, ineffective

Guideline: No Guideline Possible

Three new studies directed to transdermal fentanyl were published since the previous guideline update [44, 45] or intranasal fentanyl (Table 6) [59]. This level of evidence, however, did not raise the level of a guideline status. Furthermore, considering the stringer criteria for a guideline, the previous Suggestion was reversed for No Guideline Possible. The remaining clinical setting in which transdermal fentanyl was studied did not have new evidence, and their guideline determination is unchanged.

Other interventions or categories

For interventions that were reported in the literature prior to 2011 and since no new evidence was published since then, the 2013 guideline update rolls over to this guideline update (Table 7).

Discussion

As demonstrated by the results of this systematic review and the previous guideline update, a wide variety of agents have been evaluated for the prevention or treatment of OM secondary to cancer therapy.

These guidelines reiterate the 2013 guidelines: [1] Recommendation against sucralfate for the prevention of OM-associated pain in H&N cancer patients treated with RT; [2] Recommendation against sucralfate for the treatment of OM-associated pain in H&N cancer patients treated with RT; and [3] Recommendation against sucralfate for the treatment of OM-associated pain in solid cancer patients treated with CT. These guidelines are based on evidence showing lack of efficacy and not indicating that the agent is harmful.

We note that, due to new evidence, a previous Recommendation against sucralfate to prevent CT-associated OM was reversed to No Guideline Possible. The sucralfate data do not provide support for such a beneficial effect. The

Table 6 Studies reported for fentanyl, overall level of evidence, and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author (year)	Effective	Overall level of evidence	Guideline category	Non-RCT studies
Fentanyl	Transdermal	H&N	RT-CT	T		Y	IV	NGP	Xing (2015) [53]—4 (Y), Guo (2014) [54]—4 (Y)
			RT or RT-CT	T		N			Shaiova (2004) [47]—4 (N)
		Hematol, solid	CT	T		Y	IV	NGP	Cai (2008) [55]—4 (Y)
		Hematol	HSCT	T		N	IV	NGP	Demarosi (2004) [56]—4 (N)
			HSCT	T		Y	IV		Kim (2005) [57]—4 (Y)
			HSCT	T		Y			Strupp (2000) [58]—4 (Y)
	Intranasal	H&N	RT-CT	T		Y	IV	NGP	Bossi 2014 [59]—4 (Y-3)

Non-RCT studies keys: [3] non-RCT, [4] cohort, [5] before and after, [6] case-control studies, [7] cross-sectional, [8] case series, [11] case report, [12] expert opinion

NGP no guideline possible; *HSCT* - hematopoietic stem cell transplant; *H&N* head and neck; *RT* radiotherapy; *CT* chemotherapy; *Hematol* hematological; *ca*. cancer; *PO* per os; *P* prevention; *Y* yes, effective; *N* no, ineffective

Table 7 Interventions for which the evidence and guideline are unchanged, based on existing literature [5]

Aim	Agent	Route of administration	Patient population	Treatment modality	Guideline
P	Acyclovir	PO	Hematol	CT	NGP
P	Acyclovir	PO	H&N	RT-CT	NGP
P	Clarithromycin	PO	Hematol/solid	HSCT	NGP
T	Triclosan	Topical	H&N	RT	NGP
P	Kefir	Topical and systemic	Solid	CT	NGP
P	Iseganan	Topical and systemic	Hematol/solid	HSCT	Recommendation against
P	Iseganan	Topical and systemic	H&N	RT/RT-CT	Recommendation against
P	Povidone-iodine	Topical	H&N	RT-CT	NGP
P	Povidone-iodine	Mouthwash	Hematol	HSCT	NGP
P	BcoG—antimicrobial loz.	Topical and systemic	H&N	RT	Recommendation against
P	PTA—antimicrobial loz.	Topical and systemic	H&N	RT	Recommendation against
P	PTA—antimicrobial loz.	Topical and systemic	Hematol	HSCT	NGP
T	Tetracaine	Topical	H&N	RT-CT	NGP
T	Dyclonine	Topical	NA	RT, CT	NGP
T	MGI-209 with benzocaine	Topical	Hematol and solid	CT	NGP
T	Cocaine	Topical	H&N	RT-CT	NGP
T	Amethocaine	Topical	H&N	RT	NGP
T	Capsaicin	Topical and systemic	Solid	RT-CT	NGP
T	Methadone	Topical and systemic	Hematol	HSCT	NGP
T	Ketamine	Systemic (IV)	Hematol	CT	NGP
T	Ketamine	topical	H&N	RT-CT	NGP
T	PCA	Systemic (IV)	Hematol	HSCT	Recommendation in favor
T	Gabapentin	PO	H&N	RT-CT	NGP
T	Doxepin	mouthwash	Hematol and solid	RT/RT-CT/CT/HSCT	Suggestion in favor

NGP no guideline possible; *HSCT* hematopoietic stem cell transplant; *H&N* head and neck; *RT* radiotherapy; *CT* chemotherapy; *Hematol* hematological; *PO* per os; *P* prevention; *PCA* patient-controlled analgesia

results in the newer studies indicate however that a newer formulation of sucralfate needs further study in the management and treatment of OM. Specifically, sucralfate has a new formulation (polymerized cross-linked sucralfate) [60]; and this formational chemical change may end with other clinical efficacy.

Certain agents that are not classified as analgesics can still have analgesic properties. For example, tricyclic antidepressants such as nortriptyline and doxepin and agents like gabapentin used in neuropathic pain have been tested for the management of OM pain. In the previous review, a Suggestion was made in favor of doxepin and fentanyl. Considering the stringent criteria needed for a guideline, and the mixed study population in some of the studies, the updated guideline was reversed to No Guideline Possible. A recent RCT was published comparing doxepin with placebo and reported that doxepin was significantly superior than placebo in reducing pain level; however, this effect was short and limited and did not reach the predetermined minimal clinical importance level [50].

Considering that cancer therapy makes the oral mucosa more sensitive to physiological trauma, coating agents are designed to form a barrier that reduces irritation. During this systematic review, we found reports about a new proprietary

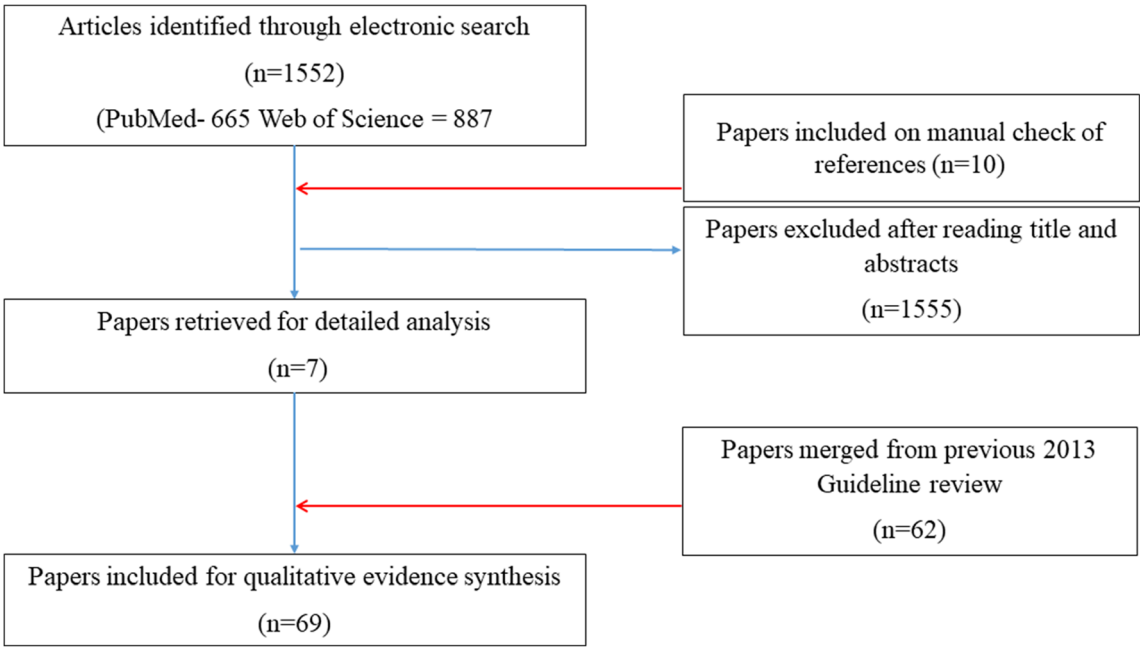

Fig. 1 Quorum diagram

viscous liquid mucoadhesive hydrogel (MAH). As there was only one publication for this agent, it was impossible to form a guideline.

There is a Suggestion for topical morphine for the treatment of OM-associated pain in H&N cancer patients treated with RT to the H&N combined with CT. In this guideline update, we clarified that this guideline refers to the combined RT-CT treatment. This is based on the fact that the major publication in this category included RT-CT patients only, and the remaining RCTs included a mix of cancer therapy protocols. This change in the guidelines compared with the 2013 guideline update is intended to link the guideline better to the evidence, and it does not preclude prescribing topical morphine for pain management in patients treated with RT to the H&N. Logically, it is likely that if topical morphine is effective for RT-CT-related OM, it will be helpful for RT-related OM, too. Further evaluation of pharmacodynamic effect is necessary. For example, three studies evaluating pain response with topical morphine concentration ranges from 0.08 for gel to 0.2–2% for rinse. The significant difference in concentration and obvious concern for toxicity with similar results require further evaluation.

The use of topical anesthetic agents is very common in patients with OM; however, studies of such agents in isolation are limited as most studies have reported of topical anesthetic in compounded rinses. With regard to the few studies of topical anesthetics alone, no new studies were identified in this update; however, as in past reviews, they all demonstrated some benefit with regard to pain relief. It is important to note the lack of high-level evidence precluded the development of any guidelines. Nevertheless, clinical experience suggests that the use of topical anesthetics can be useful in some patients to provide temporary relief and allow patients to carry out activities such as eating or oral hygiene.

A number of antimicrobial agents have been studied for OM, including antibacterial, antiviral, and antifungal agents. Overall, the results of studies of antimicrobial agents demonstrate that a secondary colonization of mucositis lesions does not seem to play a major role in the pathogenesis of OM. In this guideline update, 2 studies about antifungal agents were reviewed, which did not change the previous guideline update. This does not negate the importance of optimizing and intensifying oral care practices during the patient course of cancer therapy in order to reduce the oral inoculum, stabilize the oral pH, and reduce the risk for bacteremia.

While reviewing the literature for RCTs for the agents included in this section that were published after the cut-off date of the literature search, we identified a single study regarding a local anesthetic. This study was a small non-blinded RCT comparing the efficacy of bupivacaine lozenge and standard pain treatment on OM-associated pain in H&N cancer patients. The authors reported that pain in the oral cavity was significantly lower in the bupivacaine group than in the control group [61]. Another randomized controlled multicenter open-label study compared CAM2028 oral liquid with mucoadhesive oral rinse in cancer patients who developed OM following chemotherapy and/or radiotherapy (cancer type was not specified). The results showed that the CAM2028 oral liquid group had a significant reduction of the area under the oral mucosal pain score-time curve within 6 h of treatment compared with mucoadhesive oral rinse [62].

As highlighted by these guidelines, it is important to update clinical guidelines for prevention and treatment of OM on a systematic basis over time. Future well-designed studies are required in the prevention and treatment of oral mucositis to allow clinicians and researchers to develop evidence-based guidelines which in turn could improve clinical and economic outcomes (Fig. 1).

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Compliance with ethical standards

Conflict of interest According to the MASCC Guideline Policy, employees of commercial entities were not eligible to serve on this MASCC Guideline 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 (TR, AK, KKFC, NY, JJ, KB, MW, NBD, TK, KC, VR, AV, and SE). DPS has received research support to her institution from Galera Therapeutics. PB has served an advisory role for AstraZeneca, Helsinn, and Kyowa Kirin and received grants from Merck, Kyowa Kirin, and Roche. RVL has served as a consultant for Colgate Oral Pharmaceuticals, Galera Therapeutics, Ingalfarma SpA, 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. JE has received grants from Prysma Inc. for a funded trial.

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