



# MASCC/ISOO clinical practice guidelines for the management of mucositis: sub-analysis of current interventions for the management of oral mucositis in pediatric cancer patients

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## Abstract

**Objective** The aim of this sub-analysis was to highlight the MASCC/ISOO clinical practice guidelines for the management of oral mucositis (OM) in pediatric patients and to present unique considerations in this patient population.

**Methods** This sub-analysis of the pediatric patient population is based on the systematic review conducted by the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISSO) published in 2019/2020. Studies were scored and assigned a level of evidence based on previously published criteria. Data regarding adverse effects and compliance was collected from the original publications.

**Results** A total of 45 papers were included and assessed in this sub-analysis, including 21 randomized controlled trials (RCTs). Chewing gum was demonstrated to be not effective in preventing OM in pediatric cancer patients in 2 RCTs. The efficacy of all other interventions could not be determined based on the available literature.

**Conclusion** There is limited or conflicting evidence about interventions for the management of OM in pediatric cancer patients, except for chewing gum which was ineffective for prevention. Therefore, currently, data from adult studies may need to be extrapolated for the management of pediatric patients. Honey and photobiomodulation therapy in this patient population had encouraging potential. Implementation of a basic oral care protocol is advised amid lack of high level of evidence studies.

**Keywords** Cancer · Prevention · Treatment · Oral mucositis · Pain · Pediatric patients · Evidence-based · Guidelines

## Introduction

Oral mucositis (OM) is an important complication related to anti-neoplastic therapy, such as chemotherapy (CT), radiotherapy (RT), radio-chemotherapy (RT-CT) and hematopoietic stem cell transplantation (HSCT) [1, 2]. Pain and difficulty eating have been associated with a negative impact on the patient's quality of life [3, 4]. In addition, OM is associated

with an increased risk for systemic infections [5, 6] and high financial costs [1, 7].

The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has published clinical practice guidelines for the management of OM since 2003, with updates published in 2007, 2014 and 2019–20 [8–16]. The guidelines are presented according to the following categories of interventions: (1) anti-inflammatory; (2) antimicrobials, mucosal coating agents, anesthetics, and analgesics; (3) basic oral care; (4) cryotherapy; (5) growth factors and cytokines; (6) photobiomodulation (PBM); and (7) natural and miscellaneous agents. Studies on the interventions for gastrointestinal mucositis were reviewed too [9].

Although high-quality studies investigating OM in pediatric patients are still scarce, there has been some increase in the

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literature pertaining to this population. Therefore, it is timely to synthesize the available evidence on the management of mucositis in this sub-population.

As part of a better understanding of the MASCC/ISOO clinical practice guidelines for the management of cancer therapy-induced OM, the aim of this sub-analysis is to highlight the evidence related to OM management in the pediatric patient population and to focus on unique considerations.

## Methods

The methods related to this sub-analysis are described in detail in Ranna et al. [17]. Briefly, a literature search for relevant papers indexed from January 1, 2011, to June 2016 was conducted using PubMed and Web Science, with papers selected for review based on defined inclusion and exclusion criteria [17]. Additionally, the literature review identified manually randomized controlled trials (RCT) published until July 2019. The list of keywords used by all sections is detailed in Ranna et al. and in the respective section's articles [8–16]. Studies were scored for their level of evidence (LoE) based on Somerfield criteria [18], and flaws were listed according to Hadorn criteria [19]. 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 examined in the previous MASCC/ISOO guideline update, culminating in a systematic review of all literature until March 2020. Then, data was integrated into the guidelines based on the LoE for each intervention. Studies were grouped based on (1) the aim of the intervention (prevention or treatment of mucositis), (2) the cancer treatment modality (RT, CT, RT-CT or HSCT with or without total body irradiation (TBI), (3) the route of administration of the intervention and (4) the agent. Additionally, publications on the pediatric patient population were reviewed from each section and data about patient compliance with the treatment and adverse effects (AEs) were collected using a standard electronic form. Guidelines of this sub-analysis are presented based on the category of intervention.

## Results

The literature search identified a total of 10,195 papers from all sections, which were triaged. Following the merge with the papers included in the previous MASCC/ISOO guidelines, 340 (175 RCT) papers were included in the systematic review. For the pediatric sub-analysis, 45 papers were included, 20 RCTs, 6 comparator RCTs (randomizing to either another intervention or to an active control), 4 non-randomized

comparative (comparing an intervention to a placebo-control or no treatment), 1 cross-over, 5 before-and-after, 4 case-control, and 5 cohort studies.

## Efficacy studies on basic oral care

### Multi-agent combination oral care protocols

The preventive efficacy of combined multi-agent oral care protocols for pediatric patients with hematologic malignancies treated with CT regimens were assessed in 5 studies (1 RCT, 3 comparative studies, and 1 before-and-after study) [20–24]. The RCT [20] found no significant difference in OM incidence between the experimental group that received a combination of enhanced oral physiotherapy, use of 0.05% non-alcoholic fluoride mouthwashes daily and 20% miconazole oral gel applications ( $n = 5$ ) and the control group with no intervention ( $n = 7$ ). The findings from the 4 remaining non-RCTs [21–24] consistently indicated that the implementation of a multi-agent combination of oral care protocols is beneficial for the prevention of OM or pain during CT for pediatric cancer patients (Tables 1 and 2).

### Patient education

A single before-and-after study including hematologic and non-hematologic pediatric cancer patients ( $n = 16$ ) concluded that both the degree of OM and OM-related pain decreased ( $p < 0.05$ ) when patients were given mouth care education before CT and when they regularly performed mouth care (Tables 1 and 2) [25].

### Chlorhexidine

Three studies (2 RCTs and 1 comparative study) assessed OM outcomes in pediatric cancer patients (Tables 1, 2, 3, 4 and 5) [26–28]. The RCT, which compared 23 patients in the intervention group with 24 in a placebo group, concluded that 0.12% chlorhexidine mouthwash did not significantly reduce the incidence of OM in pediatric HSCT recipients [28]. The comparative study analyzed 14 pediatric patients (7 patients each for both the experimental and control group) treated with intensive CT regimens for hematologic malignancies and found positive results on the effectiveness of chlorhexidine 0.12% in reducing incidence of OM in the experimental group ( $p < 0.05$ ) [27]. The comparator RCT compared chlorhexidine to benzydamine and the details are given in the next paragraph under benzydamine (Tables 4 and 5) [26].

**Table 1** Studies reported for various active agents/intervention, overall level of evidence (all ages), and guideline determination (all ages)

Sections	Section/ number	Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Type of study design	Effective Y/N (key)
Basic oral care (BOC)	BOC-1	Multi-agent combination oral care protocol (A)	Topical	Hematol	CT	P	De Morales (2001)	RCT	N [1]
	BOC-2	Multi-agent combination oral care protocol (B)	Topical	Hematol	CT	P	Levy-Polack, Sebelli and Polack (1998)	Non-randomized comparative	Y [1]
	BOC-3	Multi-agent combination oral care protocol (C)	Topical	Hematol	CT	P	Cheng et al. (2001)	Before and after	Y [1] N [3]
	BOC-4	Multi-agent combination oral care protocol (C)	Topical	Hematol	CT	P	Cheng and Chang (2002)	Before and after	Y [1, 3]
	BOC-5	Multi-agent combination oral care protocol (D)	Topical	Hematol	CT	P	Chen et al. (2004)	Before-and-after	Y [1]
	BOC-6	Patient education	NA	Hematol and solid ca	CT	P	Yavuz and Yilmaz (2015)	Before-and-after	Y [1, 3]
	BOC-7	CHX	Topical (S&Sp)	Hematol and solid ca	HSCT	P	Raether et al. (1989)	RCTpb	N [1]
	BOC-8	CHX	Topical (S&Sp)	Hematol	CT	P	Costa et al. (2003)	Non-randomized comparative	Y [1, 2]
Anti-inflammatory agents	AI-1	Benzylamine	Topical (Mouthwash)	Hematol and solid ca	CT	T	Lever, Dupuis and Chan (1987)	Cross-over	N [3, 4]
	AMAA	Sucralfate	Topical (S&Sw)	Hemtol	CT	P	Shenep et al. (1988)	RCTpb	N [1] Y [3]
Antimicrobial, mucosal coating agents, anesthetics and analgesics	AMAA-2	Ketamine	Systemic (IV)	Hematol and solid ca	CT	T (pain)	James et al. (2010)	Before-and-after	Y [3]
	GF&C-1	hKGF-1 palifermin	Systemic (IV)	Hematol	HSCT	P	Lucchese et al. (2016a)	RCTpb	Y [1, 2]
Growth factors and cytokines	GF&C-2	hKGF-1 palifermin	Systemic (IV)	Hematol	HSCT	P	Lucchese et al. (2016b)	RCTpb	Y [1, 2]
	GF&C-3	hKGF-1 palifermin	Systemic (IV)	Hematol	HSCT	P	Morris et al. (2016)	Cohort	Y [1]
Natural and miscellaneous agents	GF&C-4	hKGF-1 palifermin	Systemic (IV)	Hematol	HSCT	P	Lauritano et al. (2014)	Case-control studies	Y [1, 2]
	GF&C-5	hKGF-1 palifermin	Systemic (IV)	Hematol and solid ca	HSCT	P	Czyzewski et al. (2014)	Case-control studies	Y [1, 2]
	GF&C-6	hKGF-1 palifermin	Systemic (IV)	Hematol and solid ca	HSCT	P	Vitale et al. (2014)	Case-control studies	N [1]
	GF&C-7	G-CSF	Systemic (SC)	Hematol	CT	P	Patte et al. (2002)	RCT	N [1]
	GF&C-8	GM-CSF	Systemic (IV)	Hematol and solid ca	HSCT	P	Gordon et al. (1994)	Cohort	Y [2] N [1]
	GF&C-9	TGF-β	Nutriti-on or mouthwash	Hematol and bone tumor	CT	P	de Koning et al. (2007)	RCTpb	N [1, 2]
	N&M-1	SCPR	Topical mouthwash	Hematol and solid ca	HSCT or CT	T	Raphael et al. (2014)	RCTpb, double blind	N [2, 4]
	N&M-2	Glutamine	Parenteral	Hematol	HSCT	P	Uderzo et al. (2011)	RCT, double blind	N [1, 2]

**Table 1** (continued)

Sections	Section/ number	Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Type of study design	Effective Y/N (key)
	N&M-3	Glutamine	Parenteral	Hematol	alloHSCT with/without TBI	P	Kuskonmaz et al. (2008)	Case-control study	N [1]
	N&M-4	Glutamine	Systemic (PO)	Hematol	alloHSCT with/without TBI	P	Aquino et al. (2005)	RCTpb, double blind	Y [3] N [1]
	N&M-5	Glutamine	Parenteral	Hematol	CT	P	Ward et al. (2009)	Non-randomized comparative cohort	N [1, 2]
	N&M-6	Glutamine	Parenteral	Hematol	CT	P	Yildirim et al. (2013)	Cohort	N [1, 2]
	N&M-7	Vit E	S&Sw	Hematol	CT	T	Khurana et al. (2013)	RCT, non-blinded	Y [1]
	N&M-8	Vit E	Topical	Solid ca and Hematol	CT	P	Sung et al. (2007)	RCTpb, double blind	N [1, 3]
	N&M-9	Calcitriol	Systemic (PO)	Hematol	alloHSCT HD-CT without TBI	P	Hamidieh et al. (2015)	RCTpb, double blind	N [1]
	N&M-10	Honey	Topical	Hematol	CT	T	Abdulrhman et al. (2012)	RCT	Y [2]
	N&M-11	Propolis	Topical	Hematol and solid ca	CT	T	Tomazevic and Jazbec (2013)	RCTpb, double blind	N [1, 2]
	N&M-12	Traumeel	Topical and Systemic	Hematol	Auto/alloHSCT	P	Oberbaum et al. (2001)	RCTpb, double blind	Y [1–3]
	N&M-13	Traumeel	Topical and Systemic	Hematol and solid ca	Auto/alloHSCT	P	Sencer et al. (2012)	RCTpb, double blind	N [1]
	N&M-14	Chewin gum	Topical	Hematol and solid ca	CT	P	Gandemer et al. (2007)	RCT	N [1, 2]
	N&M-15	Chewin gum	Topical	Hematol and solid ca	CT	P	Eghbali et al. (2016)	RCT	N [1]
Cryotherapy	CRY-1	Cryotherapy	Topical	Hematol and solid ca	HSCT with/without TBI	P	Sato et al. (2006)	Non-randomized comparative	Y [1]
Photobiomodulation (PBM)	PBM-1	PBM	IO	Hematol and solid ca	CT or HSCT	T	Amadori et al. (2016)	RCTpb, double blind	Y [3] N [2]
	PBM-2	PBM	IO	Hematol and solid ca	CT or HSCT	T	Chermetz et al. (2014)	Cohort	Y [2, 4]
	PBM-3	PBM	EO	Hematol and solid ca	HSCT	P	Whelan et al. (2002)	Cohort	Y [3] N [1]

Y yes; N no; NA not applicable; ND not described

Sections: BOC basic oral care; AI anti-inflammatory; AMAA antimicrobial, mucosal coating, anesthetics, and analgesics; GF&C growth factors and cytokines; N&M natural and miscellaneous agents; CRY cryotherapy; PBM photobiomodulation

Name of agent: (A) reinforcement on oral physiotherapy, non-alcoholic 0.05% fluoride and 20% miconazole oral gel; (B) sodium bicarbonate rinses, nonalcoholic chlorhexidine 0.12% rinses, cleaning of oral mucosa with iodopovidone, S&Sw nystatin 500,000 units/mL, sodium fluoride 0.05% rinses; (C) daily oral care, sodium chloride rinses, chlorhexidine 0.2% rinses; (D) tooth-brushing, normal saline, petroleum jelly for lips

CHX chlorhexidine; BZD benzydamine; *hKGF-1* keratinocyte growth factor; *G-CSF* granulocyte colony-stimulating factor; *GM-CSF* granulocyte-macrophage colony-stimulating factor; *TGF- $\beta$*  transforming growth factor- $\beta$ ; *SCPR* supersaturated calcium phosphate rinses; *Vit E* vitamin E

Route of administration: S&Sw swish and swallow; *Systemic (IV)* systemic intravenously; *Systemic (SC)* systemic subcutaneous; *PO* per os; *IO* intraoral; *EO* extraoral

Cancer: *Hemato/* hematologic malignancies; *solid ca* solid cancer

Treatment: *CT* chemotherapy; *HSCT* hematopoietic stem cell transplantation; *autoHSCT* autologous hematopoietic stem cell transplantation; *alloHSCT* allogeneic hematopoietic stem cell transplantation; *HD* high dose of chemotherapy; *TBI* total body irradiation; *auto/alloHSCTwith/withoutTBI* autologous and allogeneic hematopoietic stem cell transplantation with high dose of chemotherapy with or without total body irradiation

Indication: *T* treatment; *P* prevention

Effective: 1—mucositis severity; 2—mucositis duration; 3—pain severity; 4—pain duration

## Efficacy studies about anti-inflammatory agents

### Benzydamine

There were no RCTs comparing benzydamine to a placebo. A single RCT comparing benzydamine to chlorhexidine reported their findings in 3 publications (Tables 4 and 5) [26, 29, 30]. The aim of this RCT was the prevention of OM in pediatric patients undergoing CT for hematologic and solid cancer. The study was designed as a non-blinded cross-over trial, where each patient behaved as their own control. The results of this RCT reported benzydamine was not superior to chlorhexidine. Another small cross-over study of 4 patients assessing benzydamine for the treatment of OM in pediatric patients with hematologic malignancies and solid tumors treated with CT reported benzydamine was not effective in reducing pain (Tables 1, 2 and 3) [31]. In this study, benzydamine mouthwash was being alternated with Hospital for Sick Children (HSC) mouthwash (nystatin 7000 U/mL, lidocaine viscous 0.58 mL/mL in NaCl 0.9%) over 2 cycles.

## Efficacy studies about antimicrobials, mucosal coating agents, anesthetics, and analgesics

### Sucralfate

A single double-blind RCT assessed the effectiveness of swish and swallow suspension with sucralfate in hematological cancer pediatric patients experimental ( $n = 24$ ) and control ( $n = 24$ ) groups who underwent CT (Tables 1, 2 and 3) [32]. Patients receiving sucralfate reported less oral discomfort ( $p = 0.06$ ) but there was no statistically significant difference in pain severity between the groups.

### Polymyxin-tobramycin-amphotericin B lozenges

A single comparator study evaluated the use of topical polymyxin-tobramycin-amphotericin B lozenges ( $n = 12$ ) to a mouthwash containing diphenhydramine, and topical anesthetic in an oral suspension of aluminum hydroxide and magnesium hydroxide ( $n = 14$ ) in the treatment of OM in hematological and solid cancer pediatric patients that underwent HSCT with or without TBI (Tables 4 and 5) [33]. The OM score in the group taking polymyxin-tobramycin-amphotericin-B was significantly lower ( $p < 0.05$ ). The 2014 mucositis guidelines paper of the MASCC/ISOO reported that the clinical difference was small [34].

### Morphine

A double-blind cross-over RCT evaluating the use of morphine in pediatric patients that underwent autologous or allogeneic HSCT found no statistical difference in daily pain scores

**Table 2** Studies reported for each active agent, patient age and sample size

Sections	Section/ number	Author, Year	Name of Agent	Patient age (average $\pm$ /SD) <sup>a</sup> (mean $\pm$ range) <sup>b</sup> (median $\pm$ range) <sup>c</sup> years		Sample size
				Active	Placebo/Control	
Basic Oral Care (BOC)	BOC-1	De Morales (2001)	Multi-agent combination oral care protocol (A)	NI (4–10) <sup>b</sup>		7 5
	BOC-2	Levy-Polack, Sebelli and Polack (1998)	Multi-agent combination oral care protocol	7.4 $\pm$ 4.1 <sup>a</sup>	6.5 $\pm$ 3.7 <sup>a</sup>	60 36
	BOC-3	Cheng et al. (2001)	Multi-agent combination oral care protocol (B)	10.3 (6–17) <sup>b</sup>		21
	BOC-4	Cheng and Chang (2002)	Multi-agent combination oral care protocol (C)	11.14 (8–16) <sup>b</sup>		7
	BOC-5	Chen et al. (2004)	Multi-agent combination oral care protocol (D)	8.4 (2–17) <sup>b</sup>		30
Anti-inflammatory agents	BOC-6	Yavuz and Yilmaz (2015)	Patient education	13.87 (8–18) <sup>b</sup>		16
	BOC-7	Raether et al. (1989)	CHX 0.12%	12 (1.7–21.6) <sup>b</sup>		24 23
	BOC-8	Costa et al. (2003)	CHX 0.12%	7 (2–10) <sup>b</sup>		7 7
Antimicrobial, mucosal coating	AI-1	Lever, Dupuis and Chan (1987)	Benzylamine	6 (2–13) <sup>b</sup>		2 2
	AMAA-1	Shenep et al. (1988)	Sucralfate suspension	11.2 $\pm$ 1.6 <sup>a</sup>		24 24
	AMAA-2	James et al. (2010)	Ketamine	5.1 (0.3–13.6) <sup>b</sup>		16
Growth factors & cytokines	GF&C-1	Lucchese et al. (2016a)	hKGF-1 Palifermin	11 (7–16) <sup>c</sup>	11 (7–16) <sup>c</sup>	27 27
	GF&C-2	Lucchese et al. (2016b)	hKGF-1 Palifermin	12 (8–15) <sup>c</sup>	12 (8–15) <sup>c</sup>	24 22
	GF&C-3	Morris et al. (2016)	hKGF-1 Palifermin	I/III: 1.3 $\pm$ 0.5 (1–2y) <sup>b</sup> 6.8 $\pm$ 2.9 (3–11y) <sup>b</sup> 14.8 $\pm$ 1.3 (12–16y) <sup>a</sup> ~		9 // 9 // 9
Natural and miscellaneous agent	GF&C-4	Lauritano et al. (2014)	hKGF-1 Palifermin			20 20
	GF&C-5	Czyzewski et al. (2014)	hKGF-1 Palifermin	10.4 <sup>c</sup>	13.2 <sup>c</sup>	31 31
	GF&C-6	Vitale et al. (2014)	hKGF-1 Palifermin	7.9 $\pm$ 6.19 <sup>a</sup>	6.8 $\pm$ 5.49 <sup>a</sup>	25 33
	GF&C-7	Patte et al. (2002)	G-CSF	8 $\pm$ 4 <sup>a</sup>	9 $\pm$ 4 <sup>a</sup>	75 73
	GF&C-8	Gordon et al. (1994)	GM-CSF	8.6 (4–17) <sup>b</sup>	11.5 (3–18) <sup>b</sup>	14 12
	GF&C-9	de Koning et al. (2007)	TGF- $\beta$	8 (1–14) <sup>b</sup>		11 14
	N&M-1	Raphael et al. (2014)	SCPR	11.3 $\pm$ 3.9 <sup>a</sup>	9.9 $\pm$ 4.7 <sup>a</sup>	15 14
	N&M-2	Uderzo et al. (2011)	Glutamine	8.0 (0.9–18.6) <sup>c</sup>	8.4 (0.4–18.6) <sup>c</sup>	60 58
N&M-3	Kuskonmaz et al. (2008)	Glutamine	8.3 $\pm$ 5.2 <sup>a</sup>	6.9 $\pm$ 4.3 <sup>a</sup>	21 20	
N&M-4	Aquino et al. (2005)	Glutamine	8.9 $\pm$ 1.0 <sup>a</sup>	10.5 $\pm$ 0.6 <sup>a</sup>	57 63	
N&M-5	Ward et al. (2009)	Glutamine	8.76 $\pm$ 5.78 (2–21) <sup>ab</sup>		50 50	
N&M-6	Yildirim et al. (2013)	Glutamine	6 (3.5–10) <sup>c</sup>		30 31	

**Table 2** (continued)

Sections	Section/ number	Author, Year	Name of Agent	Patient age (average $\pm$ SD) <sup>a</sup> (mean $\pm$ range) <sup>b</sup> (median $\pm$ range) <sup>c</sup> years		Sample size
				Active	Placebo/Control	
	N&M-7	Khurana et al. (2013)	Vit E	II: 9.29 $\pm$ 2.58 <sup>a</sup> III: 9.48 $\pm$ 2.53 <sup>a</sup>	I: 8.98 $\pm$ 2.58 <sup>a</sup>	24 24 24
	N&M-8	Sung et al. (2007)	Vit E	12.7 (6.4–15.1) <sup>c</sup>		22 23
	N&M-9	Hamidieh et al. (2015)	Calcitriol	9 $\pm$ 2.7 (3–13) <sup>ab</sup>	8 $\pm$ 2.5 (4–12) <sup>ab</sup>	14 14
	N&M-10	Abdulrhman et al. (2012)	Honey	6.9 $\pm$ 3.8 (2–18) <sup>ab</sup>		30 30 30
	N&M-11	Tomazevic and Jazbec (2013)	Propolis	6.7 $\pm$ 5.3 (1–16.8) <sup>a</sup>	9.3 $\pm$ 6.6 (1–18.8) <sup>a</sup>	19 21
	N&M-12	Oberbaum et al. (2001)	Traumeel	10.1 $\pm$ 7.0 <sup>a</sup>	9.7 $\pm$ 5.7 <sup>a</sup>	15 15
	N&M-13	Sencer et al. (2012)	Traumeel	12 (3–24) <sup>c</sup>	11 (3–25) <sup>c</sup>	98 92
	N&M-14	Gandemer et al. (2007)	Chewin gum	11.6 (5.2–17.9) <sup>c</sup>	12.9 (5.2–18.7) <sup>c</sup>	73 72
	N&M-15	Eghbali et al. (2016)	Chewin gum	9 $\pm$ 2.7 <sup>a</sup>	8 $\pm$ 2.1 <sup>a</sup>	65 65
Cryotherapy	CRY-1	Sato et al. (2006)	Cryotherapy/ propantheline	NR		12 5 7
Photobiomodulation (PBM)	PBM-1	Amadori et al. (2016)	PBM	9.8 $\pm$ 3.25 <sup>a</sup>	9.2 $\pm$ 3.85 <sup>a</sup>	62 61
	PBM-2	Chermetz et al. (2014)	PBM	13 (10–17) <sup>c</sup>		18
	PBM-3	Whelan et al. (2002)	PBM	12.5 (2–23) <sup>c</sup>		32

Y: yes; N: no; NA: not applicable; NR: not reported; a: average $\pm$ SD; b: mean $\pm$  range; c: median $\pm$  range

Sections: BOC: basic oral care; AI: anti-inflammatory; AMAA: antimicrobial; mucosal coating, anesthetics, and analgesics; GF&C: growth factors and cytokines; N&M: natural and miscellaneous agents; CRY: cryotherapy; PBM: photobiomodulation

~See original publication for details



**Table 3** Studies reported for each active agent, arms, adverse events and tolerability, and patient's compliance

Sections	Section/ number	Control arm/s		Outcome measure/ scale used	Adverse events (AE) and tolerability (If reported)	Patient's compliance (if reported)		Unique considerations related to intervention in pediatric patients
		Active	Placebo/ control			Dichotomic categorical	Quantitative analysis (active vs placebo/control)	
Basic Oral Care (BOC)	BOC-1	(A)	None	1- Rutkauskas' scale (Rutkauskas et al. 1993)	NR	NR	NR	Small sample.
	BOC-2	(B)	None	1- Toh's scale (Toh et al. 1990)	N	NR	NR	Poor oral hygiene and candidiasis were statistically higher in the control arm. Incidence of OM did not differ between the studied groups, even though a significant decrease of severity was observed in the experimental group ( $p = 0.0013$ ).
	BOC-3	(C)	None	1- Modified OAG (Eilers et al. 1988) 3- Faces scale	N	Y	Adequate ( $\geq 80\%$ ) 92%, 95% and 90% in 1st, 2nd and 3rd weeks, respectively.	Mean OM incidence and score ( $p =$ 0.00002), as well as mean-related pain score ( $p = 0.0001$ ) showed statistically significant differences between control and experimental groups. The control group received more frequent opioids or local anesthetics for pain relief.
	BOC-4	(C)	None	1- Modified OAG (Eilers et al. 1988) 3- Faces scale and Wong and Baker's scale (1988)	N	Y	Adequate ( $\geq 80\%$ ) 93.36%, 96.4% and 93.82% in 1st, 2nd and 3rd weeks, respectively.	Small sample. There were statistically significant differences in the mean OM score ( $p = 0.001$ ) and related pain score ( $p = 0.006$ ) between the control and experimental groups during the study, but not in the incidence.
	BOC-5	Not specified	None	1- Modified OAG (Eilers et al. 1988)	N	Y	NR	Patients had decreased oral complications ( $p = 0.0000$ ), especially in the mucous membrane and voice categories of OAG after the oral care protocol.
	BOC-6	Patient education	None	1- WHO and ChIMES 3- ChIMES	NA	NR	NR	The actual mouth care protocol included a daily oral care program, salty water rinses, S&Sw glutamine mouthwashes, lip moisturizer.
	BOC-7	CHX 0.12%	Placebo mouth- wash	1- non-standard scale (% of injured mucosa)	None	Y	67.4 ± 28% vs 79.0 ± 21%	Placebo-treated controls showed early signs and higher early incidence of OM. Autologous and T cell-depleted BMT patients showed less severe mucositis, but did not differ between CHX and placebo groups, unlike the allogenic BMT patients.



Table 3 (continued)

Sections	Section/ number	Control arm/s		Outcome measure/ scale used	Adverse events (AE) and tolerability (If reported)	Patient's compliance (if reported)		Unique considerations related to intervention in pediatric patients
		Active	Placebo/ control			Dichotomic categorical	Quantitative analysis (active vs placebo/control)	
Anti-inflammatory agents	BOC-8	CHX 0.12%	Placebo mouth- wash	1- NR	Stinging or burning sensation	NR	NR	Small sample.
	AI-1	BZD followed by HSC mouthwash	HSC mouth- wash followed by BZD	Bruyan & Madeira (1975) (OM) / pictorial scale or VAS	Severe oral stinging	Y	NR	Both preparations reduced pain for at least one hour in most instances, but not for two hours. 3 of 4 patients elected to continue treatment with HSC mouthwash for pain. BZD: associated with pain and stinging by patient with severe OM.
Antimicrobial, mucosal coating	AMAA-1	Sucralfate suspension	Placebo suspension	1,3 - non-standard index	Cutaneous rash.	NR	NR	Gastrointestinal mucositis was also assessed but did not differ between the two groups.
	AMAA-2	Ketamine	Before Ketamine	3 - FPS-R or FLACC	Nausea/vomiting and pruritus.	NA	NA	At baseline, patients received either PCA or NCA. All 16 patients then received ketamine. 12 patients received a NCA infusion and 4 received a PCA infusion. The study reported about 33 patients; however only 16 patients were included in the before-and-after analysis of ketamine.
Growth factors & cytokines	GF&C-1	hKGF-1 Palifermin	Placebo	WHO and OMDQ	Skin rash, altered taste and sensation of increased tongue thickness.	Y	NR	60 µg/Kg/day – 3 days before and 0, +1, +2 post-HSCT
	GF&C-2	hKGF-1 Palifermin	Placebo	WHO	Skin rash, altered taste and sensation of increased tongue thickness.	Y	NR	60 µg/Kg/day – 3 days before and 0, +1, +2 post-HSCT
	GF&C-3	Palifermin-40//60// 80 µg/Kg/day		WHO	Skin rash, gingival hyperplasia, lip swelling, pharyngeal plaque and face edema.	Y	NR	The incidence of severe OM was lower in the 80 mg/kg/day dose group. All doses were well tolerated and showed a good safety profile in all three pediatric age groups
	GF&C-4	palifermin	None	WHO	Skin rash and altered taste	Y	NR	60 µg/Kg/day – 3 days before and 0,+ 1,+2 post HSCT
	GF&C-5	palifermin	None	WHO	Skin rash	Y	NR	The data on the groups is incomplete. 60 µg/Kg/day – 3 days before and 0,+1,+2 post HSCT
	GF&C-6	palifermin	None	WHO	NR	Y	NR	There are solid tumors, brain tumors and hematomas in patient. 60 µg/Kg/day – 3 days before and 0, +1, +2 post HSCT.

Table 3 (continued)

Sections	Section/ number	Control arm/s		Outcome measure/ scale used	Adverse events (AE) and tolerability (If reported)	Patient's compliance (if reported)		Unique considerations related to intervention in pediatric patients
		Active	Placebo/ control			Dichotomic categorical	Quantitative analysis (active vs placebo/control)	
Natural and miscellaneous agent	GF&C-7	G-CSF	None	WHO	None	NR	NR	The duration of neutropenia was reduced in the courses of this study. However, it is not consistently converted into clinical effects, such as the incidence of OM (grade 3). OM: 2nd end point.
	GF&C-8	GM-CSF	None	OAS and CMS	None	NR	NR	GM-CSF was effective in reducing the duration of mucositis in patients undergoing autoHSCT with TBI.
	GF&C-9	TGF- $\beta$	Placebo	WHO	None	Y	NR	Two-period cross-over: Study-mouthwash: TGF- $\beta$ 2 + CHX. One patient: withdrawal due to taste aversion.
	N&M-1	SCPR	Placebo	NCI-CTCAE v 3.0	None	Y	NR	No patients dropped out in both groups.
	N&M-2	Glutamine	None	WHO	None	NR	NR	0.4 g/kg/d, IV, started first day of BMT and ended when the patients could orally cover >50% of their daily energy requirements
	N&M-3	Glutamine	None	NR	None	NR	NR	Dose: 0.4 g/kg/d, IV, from D-9 to D + 21
	N&M-4	Glutamine	Placebo	Walsh Scale (1999)	None	Y	76.6 $\pm$ 4.2% vs 74.2 $\pm$ 4.0%	Dose: 2 g/m <sup>2</sup> /dose, twice day;
	N&M-5	Glutamine	None	NCI-CTCAE	None	Y	NR	It used the patients as their own controls. Adm.: orally or via enteral feeding; dose: 0.65 g/kg once daily for 7 day; Osteosarcoma (3), Rhabdomyosarcoma (5), Ewing's sarcoma/PNET (9)
N&M-6	Glutamine	None	WHO	None	Y	NR	Sample Size: 12 patients with 61 therapy courses (CT); it used the patients as their own controls. Dose: 4 g/kg/d, D1 of CT to D7 of CT.	
N&M-7	II: Vit E III: Pycnog-enol	I: Glycerine	None	NR	None	Y	NR	Well-tolerated Aim: I: Control, II: Vit E (200 mg/day), III: Pycnog-enol (1 mg/Kg/day); Oral Care: CHX 0.12% mouth rinse – 3 $\times$ day
N&M-8	Vit E	Placebo	WHO and Sonis (1999) / VAS	Faulty taste.	Y	NR	NR	Sample Size: 16 patients with 45 therapy courses (CT); Data on the arms and the sequence of the cycles are not clear. Patients had worse compliance with vit E

Table 3 (continued)

Sections	Section/ number		Outcome measure/ scale used	Adverse events (AE) and tolerability (If reported)	Patient's compliance (if reported)		Unique considerations related to intervention in pediatric patients
	Control arm/s Active	Placebo/ control			Dichotomic categorical	Quantitative analysis (active vs placebo/control)	
N&M-9	Calcitriol	Placebo	WHO	None	Y	NR	Prophylaxis regimen of OM: nystatin 15–20 drops every 3 h, a chewable tablet of sucralfate 500 mg every 6 h, and 10 mL diluted povidone-iodine every 3 h.; Calcitriol: 0.025 µ/day Honey group: 0.5 g honey/Kg (maximum 15 g) 3x/day until healing or for 10 day; HOPE: 0.25 g/Kg (maximum 5 g) of a 4:2:1 mixture of honey, olive oil-propolis extract and beeswax – 3/ day until healed or for 10 days; Control: benzocaine 7.5% gel (topic) – 3 × day. Flower involved in the collection was <i>Trifolium alexandrinum</i> – El Mahala, Gharbia Governorate, Egypt
N&M-10	Honey HOPE	Benzocaine 7.5% control	NCI-CTC	Transient burnig – HOPE related to propolis.	Y	NR	No AE. 0.38 g of propolis was used for each application (morning and evening). Both groups: CHX mouthwashes 2x/day; oral amphotericin B. There was no clear evidence of the beneficial effect of Traumeel in any category of compliance. Both groups: CHX mouthwashes; in one center, fungizone was widely used. In patients receiving less toxic regimens, a decrease in WHO grade 1–4 oral mucositis was noted in the gum arm compared with the standard arm (49% vs. 72%, <i>P</i> =0.03).
N&M-11	Propolis	Placebo	OAG	None	Y	NR	
N&M-12	Traumeel	Placebo	WHO	Nausea	Y		
N&M-13	Traumeel	Placebo	Walsh scale and WHO	None	Y	59.4 ± 8.3% vs 43.3 ± 9.3% of full protocol	
N&M-14	Chewin gum + Oral care	Oral care	WHO and VAS	None	Y	53/61 (chewing gum) vs NA	
N&M-15	Chewing gum + "Magic mouthwash";	"Magic mouth-wash";	WHO	NR	NR	NR	"Magic mouthwash": nystatin, diphenhydramine and aluminum. In advanced grades (3 and 4), no positive effect of chewing was seen. Allopurinol and aluminum hydroxide/magnesium hydroxide were used. GCSF systemically was used for all patients.
Cryotherapy	C + P P or C	None	I- WHO	None	Y	NR	

**Table 3** (continued)

Sections	Section/ number	Control arm/s		Outcome measure/ scale used	Adverse events (AE) and tolerability (If reported)	Patient's compliance (if reported)		Unique considerations related to intervention in pediatric patients
		Active	Placebo/ control			Dichotomic categorical	Quantitative analysis (active vs placebo/control)	
Photobiomodulation (PBM)	PBM-1	LLLT	Placebo	WHO and VAS (face)	None	NR	NR	Severe OM in 20.0% in patients in the single prophylaxis (C or P) and 42.9% patients in the control groups. SGI: C + P; SGI: P or C. Compliance: Good generally, except for some young children (quality assessment) The data on the characteristics of each group is not present in the text. LLLT: applicator –dentist; mucosal distance – NR; stationary LLLT: Applicator – NR; Mucosal distance -Defocused, rotatory motion LED: Applicator – clinicians; Extra-oral epithelium distance - within 1 cm. Aim: left cheek – study; right cheek – control
	PBM-2	LLLT	NA	WHO, VAS and quest	Burning sensation	Y	NR	
	PBM-3	LLLT	NA	Schubert OMI and Wong-Baker "smiley face" scale	NR	Y	NR	

Sections: *BOC* basic oral care; *AI* anti-inflammatory; *AMAA* antimicrobial, mucosal coating, anesthetics, and analgesics; *GF&C* growth factors and cytokines; *N&M* natural and miscellaneous agents; *CRY* cryotherapy; *PBM* photobiomodulation

Name of agent: (A) reinforcement on oral physiotherapy, non-alcoholic 0.05% fluoride and 20% miconazole oral gel; (B) sodium bicarbonate rinses, nonalcoholic chlorhexidine 0.12% rinses, cleaning of oral mucosa with iodopovidone, S&Sw nystatin 500,000 units, sodium fluoride 0.05% rinses; (C) daily oral care, sodium chloride rinses, chlorhexidine 0.2% rinses; (D) tooth-brushing, normal saline, petroleum jelly for lips; *CHX* chlorhexidine; *BZD* benzylidamine; *hKGF-1* Keratinocyte growth factor; *G-CSF* granulocyte colony-stimulating factor; *GM-CSF* granulocyte-macrophage colony-stimulating factor; *TGF-β* transforming growth factor-β; *SCPR* supersaturated calcium phosphate rinses; *Vit E* vitamin E

Outcome measure/scale used: *OAG* Oral Assessment Guide; *WHO* World Health Organization; *ChIMES* Children's International Mucositis Evaluation Scale; *FPS-R* Faces Pain Scale-Revised; *FLACC* face, legs, activity, cry, consolability; *OAS* Oral Assessment Score; *CMS* Composite Mucositis Score; *NCI-CTCAE* National Cancer Institute - Common Terminology Criteria for Adverse Events; *OMAS* Oral Mucositis Assessment Scale; *VAS* visual analogue scale; *OMI* oral mucositis index

*Quest* questionnaire; *OMDQ* Oral Mucositis Daily Questionnaire

Unique considerations: *AE* adverse effects; *PNET* primitive neuroectodermal tumor; *LLLT* low-level laser therapy; *LED* light emitting diode

**Table 4** Comparator studies for various agents, overall level (all ages), and guideline determination (all ages)

Sections	Section/ number	Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Type of study design (key)	Effective Y/N (key)
Anti-inflammatory agents	AI-2	BZD/CHX	Mouthwash	Hematol and solid ca	CT	P	Cheng (2004)	RCT	N [1, 3]
	AI-3	BZD/CHX	Mouthwash	Hematol and solid ca	CT	P	Cheng, Chang Yuen (2004)	RCT	N [1]
	AI-4	BZD/CHX	Mouthwash	Hematol and solid ca	CT	P	Cheng & Chang (2003)	RCT	N [1, 3]
Antimicrobial, mucosal coating agents, anesthetics and analgesics	AMAAA-3	PTA vs. BMA	Topical lozenges vs topical mouthwash	Hematol and solid ca	HSCT with or without TBI	T	Bondi et al. (1997)	RCT	Y [1]
	AMAAA-4	Morphine and hydromorphone (MHM vs. HMMH)	Systemic (IV)	Hematol ca	HSCT without TBI	T	Collins et al. (1996)	RCT double-blind three-period crossover	Y [3]
	AMAAA-5	Morphine (PCA vs. CI)	Systemic (IV)	Hematol ca	HSCT with TBI	T	Mackie, Coda and Hill (1991)	RCT	Y [3]

Y yes; N no

Section: AI anti-inflammatory agents; AMAA antimicrobial, mucosal coating agents, anesthetics and analgesics

Name of Agent: CHX chlorhexidine; BZD benzzydamine; PTA polymyxin-tobramycin-amphotericin B; BMA Benadryl® (diphenhydramine)-Maalox® (magnesia-alumina)-anesthetic (2% lidocaine gel);  
MHM morphine, hydromorphone, morphine (order), HMMH hydromorphone, morphine, hydromorphone (order)

Cancer: Hemato/ hematologic malignancies; solid ca solid cancer

Route of administration; Systemic (IV) systemic intravenously; PCA patient-controlled analgesia; CI continuous infusion

Treatment: CT chemotherapy; HSCT hematopoietic stem cell transplantation; TBI total body irradiation

Indication: P prevention; T treatment

Study design key: RCT randomized controlled trial

Effective: 1—mucositis severity; 2—mucositis duration; 3—pain severity; 4—pain duration

**Table 5** Comparator studies for various agents, arms, adverse events and tolerability, and patient's compliance

Sections	Section/ number	Author, year	Name of agent	Patient age (average ± SD) <sup>a</sup> (mean ± range) <sup>b</sup> years		Sample size		Control arm/s		Outcome measure / scale used	Adverse events (AE) and tolerability (if reported)	Patient's compliance	Unique considerations related to intervention in pediatric patients
				Active I	Active II	Active I	Active II	Active I	Active II				
Anti-inflammatory agents	AI-2	Cheng (2004)	BZD vs CHX	10.3 (6–16) <sup>b</sup>	17	17	CHX follo- wed by BZD	BZD follo- wed by CHX	OAG	Stinging or burning sensation and taste alteration.	Y	94 ± 4.8% (BZD) vs 91 ± 4.2% (CHX)	Children's acceptance and tolerance of CHX 0.2% and BZD 0.15%. Both agents were well-tolerated* Effectiveness of CHX 0.2% and BZD 0.15% in preventing OM. **
	AI-3	Cheng, Chang Yuen (2004)	BZD vs CHX	10.3 ± 3.3 (6–16) <sup>ab</sup>	17	17	CHX follo- wed by BZD	BZD follo- wed by CHX	OAG	Stinging or burning sensation	Y	93.2 ± 5.8% (BZD) vs 92.6 ± 5.3% (CHX)	Effectiveness of CHX 0.2% and BZD 0.15% in preventing OM. **
	AI-4	Cheng & Chang (2003)	BZD vs CHX	10.35 ± 3.02 3.7 <sup>a</sup>	17	17	CHX follo- wed by BZD	BZD follo- wed by CHX	WHO and VAS	Stinging or burning sensation and taste alteration.	Y	93.2 ± 5.8% (BZD) vs 92.6 ± 5.3% (CHX)	Effectiveness of CHX 0.2% and BZD 0.15% in alleviating OM symptoms. * Dilution of BZD and CHX was required in 3% and 6%, respectively.
	AMAA-3	Bondi et al. (1997)	PTA/BMA	7.06 (1.1–15.7) <sup>b</sup>	12	14	PTA	BMA	Modified Spijkervet's index (1989)	NR	NR	NR	Patients received total parenteral nutrition, and dental hygiene was performed by an oral hygienist. CHX mouthwash was used daily. Patients switched opioids on each period of three days. The 2 groups differed in order of opioids
Antimicrobial, mucosal coating agents, anesthetics and analgesics	AMAA-4	Collins et al. (1996)	Morphine/ hydromorphone	13.7 <sup>b</sup>	5	5	MHM	HMH	VAS	Mild sedation, nausea, vomiting, pruritus and urinary retention	NA	NA	Patients switched opioids on each period of three days. The 2 groups differed in order of opioids

**Table 5** (continued)

Sections	Section/ number	Author, year	Name of agent	Patient age (average ± SD) <sup>a</sup> (mean ± range) <sup>b</sup> years		Sample size		Control arm/s		Outcome measure / scale used	Adverse events (AE) and tolerability (if reported)	Patient's compliance		Unique considerations related to intervention in pediatric patients
				Active I	Active II	Active I	Active II	Active I	Active II			Dichotomic categorical	Quantitative analysis	
AMAA-5	Mackie, Coda and Hill (1991)	Morphine	13.6 ± 0.6 <sup>a</sup>	14.8 ± 0.5 <sup>a</sup>	10	10	PCA	CI	VAS	Mild nausea, trouble paying attention and keeping awake during adminis- tered protocol.	NA	NA	Repeated Measures: ANOVA did not show any significant difference in the pain scores reported by the 2 groups.	

Y yes; N no; NA not applicable; NR not reported; <sup>a</sup> average ± SD; <sup>b</sup> mean ± range

Section: AI anti-inflammatory agents; AMAA antimicrobial, mucosal coating agents, anesthetics and analgesics

Name of Agent: CHX chlorhexidine; BZD benzzydamine; PTA polymyxin-tobramycin-amphotericin B; BMA Benadryl® (diphenhydramine)-Maalox® (magnesia-alumina)-anesthetic (2% lidocaine gel); MHH morphine, hydromorphone, morphine (order), HMM hydromorphone, morphine, hydromorphone (order)

PCA patient-controlled analgesia; CI continuous infusion outcome measure/scale used: OAG Oral Assessment Guide; WHO World Health Organization; VAS Visual Analogue Scale

\*Cheng & Chang (2003), Cheng (2004) and Cheng, Chang Yuen (2004) have similar design and population



**Table 6** Studies addressing photobiomodulation for the management of oral mucositis in pediatric patients

Cancer treatment modality	Aim	Author, year	Cancer type	PBM source	Wave-length (nm)	Power (mW)	Fluence (J/cm <sup>2</sup> )	Time (s)	Irradiance (mW/cm <sup>2</sup> )	Spots (cm)	Number of spots	Distance from tissue	Number of sessions	Irradiation	Effective Y/N (key)
CT	T	Amadori (2016)	Hematol, solid ca and HSCt	DioLas (GaAlAs)	830	150	4.5	30	1	1	ND	ND	4	Stationary	Y [3] N [2]
CT or HSCT	T	Chernetz (2014)	Hematol and solid ca	DioLas (GaAlAs)	970	5000		230	1	1	ND	Defocused	4 (twice a day)	Rotator motion	Y [2, 4]
Auto/allo HSCT with/without TBI	P	Whelan (2002)	Hematol and solid ca	LED	670		4	71	56		1	Within 1 cm	ND	Stationary	Y [3] N [1]
CT or HSCT	T	Vitale (2017)*	Hematol	DioLas (GaAlAs)	970	3200		230	1	1	9 sites, each had multiple spots	Defocused	4	Rotatory motion	Y [1–4]
CT or CT-RT	T	Medeiros-Filho (2017)*	*Hematol and solid ca	DioLas (InGaP and GaAlAs)	660//808 + 660	100		90//10			ND	1 cm above the lesion	4	Stationary	N [1]
CT	T	Ribeiro da Silva (2018)*	Hematol and solid ca	DioLas (InGaAlP)	660	100	35 or 107	10 or 30		0.028	ND (total size of the lesion: 1 per cm <sup>2</sup> )	Minimum distance from the tissue	ND	Stationary	N [1–3]
CT	T	Gobbo (2018)*	Hematol and solid ca	DioLas (InGaAlP and GaAlAs)	660 and 970	3200	36.8	25	320	1	9	Defocused	4	Rotatory motion	Y [1, 3]
CT	T	Leite Cavalcanti (2018)*	Hematol and solid ca	DioLas (InGaAlP and GaAlAs)	660 or 660 + 808	100	3.3	10		0.03	8 sites, each had multiple spots (31 points)	ND	ND	Stationary	Y [1, 2]

Y yes; N no; ND not described; ca cancer; PBM photobiomodulation; DioLas diode laser; LED light emission diode; InGaP indium-gallium-potassium; InGaAlP indium-gallium-aluminum-phosphide; GaAlAs gallium-aluminum-arsenide

Indication: T treatment; P prevention

Cancer: Hematol/ hematologic malignancies; solid ca solid cancer; HSCT hematopoietic stem cell transplantation

Treatment: CT chemotherapy; HSCT hematopoietic stem cell transplantation; auto/allo HSCT with/without TBI autologous and allogeneic hematopoietic stem cell transplantation with high dose of chemotherapy with or without total body irradiation

Effective: 1—mucositis severity; 2—mucositis duration; 3—pain severity; 4—pain duration

\*Publications included in the guidelines paper as “late breaking news”

between the compared groups (Tables 4 and 5) [35]. There were two groups that differed in the orders of the interventions. The first group was composed of pediatric patients that received morphine followed by hydromorphone and then morphine ( $n = 5$ ). The second group initiated the protocol with hydromorphone followed by morphine and then hydromorphone ( $n = 5$ ), both delivered as patient-controlled analgesia (PCA) protocol. A second RCT evaluated pediatric patients that underwent HSCT with or without TBI and compared OM-related pain outcomes between a PCA protocol and a continuous infusion regimen (Tables 4 and 5) [36]. It concluded that there was a significantly lower morphine intake in the PCA group ( $p < 0.01$ ), but there was no difference in pain intensity between the two groups.

### Ketamine

A single before-and-after study [37] analyzed the addition of ketamine to morphine PCA or nurse-controlled analgesia (NCA) protocols in regard to OM-related pain relief. This study showed that ketamine added either to a PCA or NCA protocol improved analgesic efficacy in pediatric patients with hematologic and solid malignancies that underwent variable CT regimens ( $p = 0.01$ ) (Tables 1, 2 and 3).

## Efficacy studies about growth factors and cytokines

### Keratinocyte growth factors

A single RCT, published in 2 parts, about intravenous (IV) keratinocyte growth factors (KGF-1) to prevent OM in pediatric patients undergoing HSCT reported the results of 27 patients treated with either IV KGF-1 or placebo (Tables 1, 2 and 3) [38, 39]. This RCT showed effectiveness in reducing the severity ( $p = 0.03$ ) and duration of OM ( $p < 0.001$ ). Three other studies (1 cohort [40] and 3 case-control studies [41–43]) reported that KGF-1 was effective in reducing mucositis severity or duration, and that patients complied well.

### Granulocyte colony-stimulating factor

A single RCT studied the effect of subcutaneous (SC) granulocyte colony-stimulating factor (G-CSF) included 148 pediatric patients with hematologic malignancies treated with high-dose CT. The results indicated that the use of G-CSF was ineffective to prevent severe OM (Tables 1, 2 and 3) [44].

### Granulocyte-macrophage colony-stimulating factor

There is limited evidence for the use of IV granulocyte-macrophage colony-stimulating factor (GM-CSF) in pediatric patients undergoing HSCT for the prevention of OM

(Tables 1, 2 and 3) [45]. This cohort reported of non-significant reduction in duration of OM.

### Transforming growth factor- $\beta$ —nutrition or mouthwash

A single RCT on the use of transforming growth factor- $\beta$  (TGF- $\beta$ ) for the prevention of OM in 25 pediatric patients treated with CT (Tables 1, 2 and 3) [46] concluded that TGF- $\beta$  is not effective for the prevention of CT induced OM.

## Efficacy studies about natural and miscellaneous agents

### Supersaturated calcium phosphate rinse

A single RCT of 29 pediatric patients undergoing HSCT or CT reported the efficacy of supersaturated calcium phosphate rinse (SCPR) (Caphosol®, EUSA Pharma, Hemel Hempstead, UK) for the treatment of OM. The study reported that SCPR is ineffective for the treatment of OM in alleviating severity, duration, and pain severity (Tables 1, 2 and 3) [47].

### Glutamine

A single RCT including 118 patients [48] and a case-control study [49] that assessed the efficacy of parenteral glutamine in pediatric patients reported no beneficial effect of glutamine (parenteral) for prevention of OM in HSCT (Tables 1, 2 and 3). Contrary to this a single RCT on oral glutamine based on the [50] same patient population ( $n = 120$ ) showed glutamine to be effective in reducing pain duration ( $p = 0.01$ ) and to have a tendency to reduce OM severity. Further, some studies with lower quality designs reported that parenteral glutamine was ineffective in the prevention of OM in patients with hematologic cancer treated with CT [51, 52].

### Vitamin E

A single RCT compared topical vitamin E to a placebo for the prevention of OM in hematologic malignancies and solid cancer patients treated with CT failed to demonstrate a reduction in OM severity (Tables 1, 2 and 3) [53]. The sample size was 16 patients; however, it is unclear how many patients were in each arm since data was reported per treatment cycle.

Another RCT that evaluated the efficacy of swish and swallow vitamin E compared with pycnogenol or glycerin (vehicle-control) in 72 pediatric patients treated with CT (Tables 1, 2 and 3) [54] reported no significant difference between both active arms. However, the two active arms were effective compared with the control arm for the treatment of OM ( $p < 0.001$ ).

### Calcitriol

A single RCT described the use of calcitriol for the prevention of OM in 28 patients undergoing HSCT due to Fanconi anemia (Tables 1, 2, and 3) [55]. The study did not report considerable benefits for calcitriol in preventing OM.

### Honey

A single placebo-controlled RCT of topical honey for the treatment of OM in 90 pediatric patients with hematologic malignancies undergoing CT (Tables 1, 2 and 3) [56] reported the effectiveness of the *Trifolium alexandrinum*-based honey in reducing the healing time of ulcerative OM. ( $p = 0.0005$ ). Additionally, a mixture of honey, olive oil-propolis extract, and beeswax (HOPE) was significantly more effective than in the control ( $p = 0.0056$ ).

### Propolis

A single RCT reported the ineffectiveness of topical propolis for the treatment of OM in pediatric patients ( $n = 40$ ) treated with CT for hematological and solid cancers (Tables 1 and 2) [57].

### Traumeel

Two RCTs investigated the use of Traumeel for the prevention of OM in pediatric patients undergoing HSCT (Tables 1, 2 and 3) [58, 59]. The pediatric patients were instructed to swish and swallow in both studies. In the first RCT with hematologic patients ( $n = 30$ ), Traumeel illustrated a significant reduction in the severity and duration of OM ( $p < 0.01$ ) [58]. On the other hand, in the second RCT, Traumeel was ineffective for the prevention of OM in pediatric patients with hematologic and solid cancers ( $n = 181$ ) [59].

### Chewing gum

Two RCTs described the use of chewing gum for the prevention of OM in pediatric patients treated with CT for hematologic malignancies and solid cancers (Tables 1, 2 and 3) [60, 61]. In one RCT with 145 pediatric patients, oral care alone was compared with oral care combined with a chewing gum routine [61]. In the other RCT with 130 pediatric patients, the use of chewing gum and “magic mouthwash” (nystatin, diphenhydramine, and aluminum) was compared with “magic mouthwash” alone [60]. Both studies reported chewing gum was not effective to prevent OM.

### Pycnogenol

A single RCT reported on pycnogenol compared with vitamin E or a control group and results are presented under the “Vitamin E” section above [54].

### Efficacy studies on cryotherapy

One study evaluated the effectiveness of cryotherapy together with the vasoconstrictor propantheline ( $n = 12$ ), compared to a single intervention (cryotherapy or propantheline;  $n = 5$ ) and to a control group receiving no treatment ( $n = 7$ ) for the prevention of OM in pediatric patients undergoing HSCT with or without TBI (Tables 1, 2 and 3) [62]. Cryotherapy was applied 5–10 min before and at least 30 min following the CT infusion. Propantheline was administered at 1.5 mg/kg once daily from the day before CT infusion until one day before the HSCT. The results showed that the combination protocol was significantly more effective in reducing the incidence of severe OM (grades 3–4) compared to the other two groups ( $p = 0.0069$ ).

### Efficacy studies on PBM

The management of OM with intra-oral PBM in a mixed pediatric patient population, including hematologic malignancies and solid cancers, treated with either high-dose CT or HSCT has been described by two studies (Tables 1, 2, 3 and 6) [63, 64]. The RCT with 123 pediatric patients observed the effectiveness of intra-oral PBM in pain reduction ( $p < 0.005$ ) [63]. A cohort study ( $n = 18$ ) with intra-oral PBM therapy reported a significant decrease in the severity of OM ( $p < 0.05$ ) and pain reduction ( $p < 0.001$ ) [64].

Another cohort study on the effectiveness of extra-oral PBM for the prevention of OM in a mixed pediatric patient population ( $n = 32$ ), including hematologic malignancies and solid cancers treated with HSCT was reported (Tables 1, 2 and 3) [65]. The results demonstrated a significant reduction in OM-associated pain.

### AEs and tolerability

The active agents used in this sub-analysis were generally well tolerated by pediatric patients (Table 3). Interventions for which AEs were reported are detailed below.

### Chlorhexidine and benzydamine

Chlorhexidine (0.12–0.2%) and benzydamine (0.15%) have been related to stinging or burning sensations [26, 27, 29, 30]. In an RCT, the dilution of the chlorhexidine and benzydamine mouthwashes with saline or water was required in 6% and 3% of patients, respectively [30]. In another RCT,

once OM developed, there was an increase in patients who required dilution of chlorhexidine and benzydamine due to stinging and burning sensations in the oral cavity to 33% and 20% of patients, respectively [29]. Nevertheless, no patient discontinued the use of mouthwashes with both active agents. On the other hand, a small study reported severe oral stinging when benzydamine (0.15%) mouthwash was administered, and 3 out of 4 patients dropped out of the study due to this adverse effect [31].

In addition, a minor taste alteration has been reported by pediatric patients when using chlorhexidine (0.2%) and benzydamine (0.15%); in 6% and 3–9% of patients, respectively [29, 30].

### Propolis

A transient burning sensation has been reported by 26.7% of pediatric patients immediately after application of a HOPE mixture [56].

### Photobiomodulation

A burning sensation was reported following PBM therapy in 50% of pediatric patients (9 out 18) [64]. Other studies did not report any AEs.

### KGF-1

AEs related to KGF-1 were skin rash (22–44% of patients) [38–42], altered taste (10–20%) [38, 39, 42], gingival hyperplasia (11%) [40], a sensation of increased tongue thickness (12.5–16%) [38, 39], lip swelling (11%) [40], pharyngeal plaque (11%) [40], and face edema (11%) [40].

### Sucralfate

Eight (33.3%) patients that received a placebo suspension and 4 (16.6%) patients that received a swish and swallow sucralfate suspension experienced cutaneous rash [32].

### Morphine and hydromorphone

Patients that underwent a cross-over of morphine and hydromorphone reported mild sedation, nausea, vomiting, and pruritus during the administration of the protocol. Also, 1 patient presented with urinary retention during hydromorphone use, which required urinary catheterization [35]. The single administration of morphine by a PCA or continuous-infusion was associated with mild nausea, concentration issues, and sleepiness during both administered protocols [36].

### Ketamine

There was an overall incidence of nausea/vomiting and pruritus related to ketamine in 58% and 34% of patients, respectively. One patient had the ketamine withdrawn after becoming acutely confused during a septic episode and required intensive care [37].

### Vitamin E

Vitamin E was associated with an uncomfortable “oily texture” by 12 out of 16 patients in a single RCT [53].

### Compliance with treatment

The compliance was reported in 31 out of 45 of the papers (Tables 3 and 5). The compliance of pediatric patients was based on patient self-reports or parental reports. Studies reported compliance as a dichotomic categorical variable (good/poor) [21, 31, 38–43, 46, 47, 51–59, 62, 64, 65] or as a quantitative analysis [22, 23, 26, 28–30, 50, 59, 61].

Compliance was adequate in most of the studied patients, except for some cases. For example, there was a limitation specific to younger children to stay awake during oral cryotherapy application when it was performed in the evening [62].

## Discussion

This sub-analysis paper of the MASCC/ISOO clinical practice guidelines for the management of mucositis presented the available evidence regarding interventions for OM in pediatric cancer patients. Although over a dozen studies were large RCTs, the type and quality of the study design, as well as the volume of the studies are not as robust as the evidence in the adult patient population, except for chewing gum. Furthermore, the diversity of the pediatric cancer patients population in these studies, and the combination of experimental agents in a single study protocol, compromise the conclusion about an effective intervention for oral mucositis. Therefore, interventional protocols in pediatric patients need to rely on extrapolation from the currently available evidence for adult cancer patients.

The literature included in this sub-analysis reported of either oral or systemic drug-related AEs. Benzydamine or chlorhexidine necessitates dilution or dose reduction [29, 30]. Drug withdrawal was infrequently needed for benzydamine or ketamine [31, 37]. Notwithstanding, parenteral glutamine was reported to be associated with increased relapse and mortality in adult HSCT patients [66].

In the pediatric oncology setting, specific instruments may be helpful to assess OM and OM-related pain. Depending on



the age of the patient, language development, emotional difficulty in expressing themselves, comprehensive skills, and attention capacity, it can be difficult to apply the conventional scales used for adult cancer patient assessment [67]. Some examples such as the Children's International Mucositis Evaluation Scale [25, 54], a self-reporting scale designed for children with cancer, as well as visual "smiley face" scales, are validated and reliable tools for this population [22, 23, 31, 37, 54, 63, 65]. Among the selected studies in the current sub-analysis, several types of assessment tools were used, and only some of them were adapted for children.

The effectiveness of an experimental intervention relies on its capacity to prevent or mitigate the signs and symptoms of OM, as well as on its acceptance. The acceptance is driven by ease of use and lack of AEs, psycho-emotional state, and general health condition of the patient [29, 62]. In order to overcome the challenges related to pediatric patient acceptance, unique treatment strategies should be employed. For example, the use of popsicles instead of ice or ice water for younger patients undergoing oral cryotherapy may increase compliance during the application [62]. Likewise, extra-oral PBM may be tolerated better than the intra-oral approach [65, 68, 69]. Studies in cancer and non-cancer pediatric patients suggested strategies utilizing cognitive-behavioral approaches may help to handle stressful situations and consequently enhance engagement in children. For example, the use of storyboards, gaming, virtual-reality experiences, medical clowning, animal-assisted therapy, or a parent-guided therapy approach [70–75].

Following the timeframe of the literature search of the MASCC/ISOO guidelines update, 15 RCTs were published addressing interventions for the management of OM in pediatric cancer patients. The new RCTs investigated the use of natural & miscellaneous agents [76–82], PBM therapy [68, 83–86], oral cryotherapy [87], G-CSF [88], and KGF-1 vs. chlorhexidine mouthwashes [89]. These newer RCTs suggest efficacy for honey and inefficacy for SCPR. The PBM studies had conflicting results and, due to the diverse PBM protocols, it is impossible to conclude about a preferred PBM setting. The long-term effects of these interventions are unknown. Although the speculative benefit of honey on OM prevention, some concerns about an increased risk of dental caries still remains [14].

In summary, this is the first focused view of MASCC/ISOO on guidelines for the management of OM for pediatric patients. It is a detailed sub-analysis of the guidelines that were developed by this group [90]. There is evidence that chewing gum does not prevent OM. In addition, there is intriguing evidence regarding the efficacy of PBM and honey. Despite the absence of high evidence studies, the implementation of basic oral care protocol is very appropriate.

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## Compliance with ethical standards

**Conflict of interest** PRA has received grants and personal fees from PhotomedTech, personal fees from Kerber Applied Research, personal fees from Seaborough, personal fees from Shepherd University, non-financial support from National Institute of Aging, NIH, personal fees from Curalaser, personal fees and non-financial support from Vielight, personal fees from Zoovv, non-financial support from Thor Photomedicine, non-financial support from Weber Medical, non-financial support from K laser (Summa), non-financial support from Biolase, non-financial support from Irradia, non-financial support from Quasar Biotech, and non-financial support from Light scalpel, outside the submitted work; In addition, PRA has a patent light-based dental systems issued.

PB has served an advisory role for Merck Serono, Sanofi, Merck Sharp & Dohme, Sun Pharma, Angelini, Astra Zeneca, Bristol-Myers-Squibb, Helsinn, and GSK and received grants from Merck, Kyowa Hakko Kirin, and Roche. WMS, WGS, YZ, NY, ARAA, CHLH, AA, DPS, MEC, JB, KKFC, WJET, and SE declare that they have no conflict of interest.

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