



Systematic review of natural and miscellaneous agents for the management of oral mucositis in cancer patients and clinical practice guidelines—part 1: vitamins, minerals, and nutritional supplements

Noam Yarom^{1,2} · Allan Hovan³ · Paolo Bossi⁴ · Anura Ariyawardana^{5,6} · Siri Beier Jensen⁷ · Margherita Gobbo⁸ · Hanan Saca-Hazboun⁹ · Abhishek kandwal¹⁰ · Alessandra Majorana¹¹ · Giulia Ottaviani⁸ · Monica Pentenero¹² · Narmin Mohammed Nasr¹³ · Tanya Rouleau¹⁴ · Anna Skripnik Lucas¹⁵ · Nathaniel Simon Treister^{16,17} · Eyal Zur¹⁸ · Vinisha Ranna¹⁹ · Anusha Vaddi²⁰ · Karis Kin Fong Cheng²¹ · Andrei Barasch²² · Rajesh V. Lalla²³ · Sharon Elad²⁰ · 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 natural and miscellaneous agents 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 78 papers were identified within the scope of this section, out of which 29 were included in this part, and were analyzed with 27 previously reviewed studies. A new Suggestion was made for oral glutamine for the prevention of OM in head and neck (H&N) cancer patients receiving radiotherapy with concomitant chemotherapy. The previous Recommendation against the use of parenteral glutamine for the prevention of OM in hematopoietic stem cell transplantation (HSCT) patients was re-established. A previous Suggestion for zinc to prevent OM in H&N cancer patients treated with radiotherapy or chemoradiotherapy was reversed to No Guideline Possible. No guideline was possible for other interventions.

Conclusions Of the vitamins, minerals, and nutritional supplements studied for the management of OM, the evidence supports a Recommendation against parenteral glutamine in HSCT patients and a Suggestion in favor of oral glutamine in H&N cancer patients for the management of OM.

Keywords Oral mucositis · Natural · Herbal medicine · Glutamine · Zinc · Supersaturated calcium phosphate rinse · Guidelines

Introduction

Oral mucositis (OM) is a debilitating complication of cancer therapy, that in addition to pain, nutritional and psychosocial

consequences can lead to treatment delays, breaks, and dose reductions, potentially influencing treatment outcomes [1]. Therefore, extensive research has been conducted to find a remedy for OM.

Natural remedies, including herbal extracts (botanicals) and dietary supplements, have been a topic for prolific research in OM. Nutritional supplements are perceived as a needed element in patients with an unbalanced diet. Likewise, many herbal agents are considered to promote wound healing or to have analgesic effects.

✉ Noam Yarom
Noam.yarom@sheba.health.gov.il

Extended author information available on the last page of the article

The Mucositis Study Group (MSG) of the Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (MASCC/ISOO) has published clinical practice guidelines for OM [2–4]. In the 2014 guidelines update, the Natural and Miscellaneous section concluded the systematic review with 2 guidelines regarding vitamins, minerals, and nutritional supplements: (1) a Suggestion to use systemic zinc supplement to prevent OM in cancer patients receiving RT or RT-CT and (2) a Recommendation against the use of intravenous glutamine for the prevention of OM in patients receiving high-dose CT prior to hematopoietic stem cell transplantation (HSCT). No guideline was possible for any other agent [5, 6]. The aim of this project was to review newly acquired evidence and update the clinical practice guidelines for the use of natural and miscellaneous agents for the prevention and/or treatment of OM.

Methods

The methods are described in detail in Ranna et al. [7]. Briefly, a search for relevant papers indexed in the literature from January 1, 2011, to June 30, 2016, was conducted using PubMed/Web of Science/EMBASE, with papers selected for review based on defined eligibility 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 the Somerfield criteria, [8] and flaws were listed according to the Hadorn criteria [9]. 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 HSCT); and (3) the route of administration of the intervention.

The list of intervention keywords used for the literature search of the Natural and Miscellaneous section is presented in the Methods paper [7].

This report will cover the interventions categorized as vitamins, minerals, and nutritional supplements. The remaining agents will be described in the systematic review of Natural and Miscellaneous Agents for the Management of OM in Cancer Patients—Part 2.

Results

A total of 2653 papers were identified in the literature search: 1863 from PubMed and 790 from Web of Science. After careful assessment of the abstracts, 2563 articles were excluded due to repetition across databases, non-clinical studies, meta-analyses, and reviews. Three additional papers were transferred from other sections of the guidelines update. Ninety-three articles were retrieved for final review. After review of these full papers, 6 were moved to other sections, and 9 were excluded based on the eligibility criteria. A total of 78 papers are included in this section out of which 29 are included in this paper (part 1). These publications described 8 vitamins, minerals, and nutritional supplements and included in this part. These 29 new papers were merged with 27 publications that were reviewed in the previous guidelines update.

Zinc

Zinc is a vital electrolyte for homeostasis and is involved in biologic processes such as growth, wound healing, and immune reaction. Zinc is available in various forms, including zinc sulfate, zinc aspartate, and zinc L-carnosine. It is available commercially in combinations with other vitamins and elements. The specific compound affects the biologically available zinc dose. Table 1 summarizes the details of studies reviewed on zinc.

Zinc (systemic): H&N cancer, RT/RT-CT—prevention Guideline: No guideline possible (LoE I)

The efficacy of systemic zinc administration for the prevention of OM in H&N cancer patients receiving RT or RT-CT was studied in 6 randomized controlled trials (RCT). Of these, 4 reported that zinc was effective for the prevention of OM [10, 13, 15, 18] and 2 reported that zinc was ineffective [16, 17]. In these studies, the RT dose ranged between 50 and 70 Gy and exceeded 60 Gy in most patients. However, reports were not comparable in terms of type of zinc preparations and doses. Zinc sulfate was used in 4 RCTs of which zinc was found to be effective in 2 RCTs [10, 18] and ineffective in the other 2 [16, 17]. The doses administered in these RCTs ranged between 90 and 150 mg/day elemental zinc [10, 16–18]. Zinc magnesium aspartate (75 mg per day) was found to be effective in the prevention of OM in a well-designed RCT and its subsequent sub-analysis [13, 14]. Zinc L-carnosine, a zinc-containing molecule, was found effective in preventing OM compared with 4% sodium gualenate hydrate mouthwash [15].

The efficacy of systemic zinc in preventing OM in H&N cancer patients was also evaluated in 2 case-control studies demonstrating conflicting results [11, 12].

Table 1 Studies reported for zinc, 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
Zinc	PO	H&N	RT/RT-CT	P	Ertekin 2004 [10]	Y	I	NGP	–	Doi 2015 [11] – 6 (Y) Suzuki 2016 [12] – 6 (N)
					Lin 2006 [13]	Y				
					Sub-analysis in Lin 2010 [14]					
					Watanabe 2010 [15]	Y				
PO	Hematol	HSCT	P	Mansouri 2012 [19]	N	II	NGP	–	Hayashi 2014 [20] – 6 (N)	
				Arbabi-Kalati 2012 [21]	N					
				Mehdipour 2011 [22]	N					
PO	Hematol and solid ca.	CT	P		N	III	NGP	–		
Topical	Hematol	CT	P		N	III	NGP	–		

Non-RCT studies key: 3. non-RCT, 4. cohort, 5. before and after, 6. case-control studies, 7. cross-sectional, 8. case series, 9. case report, 10. expert opinion

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; NGP, no guideline possible

Based on the evaluation of the quality of studies, the LoE is rated as I. Due to conflicting data about the efficacy, no guideline was possible.

Zinc (systemic): HSCT—prevention

Guideline: No guideline possible (LoE II)

There was a single RCT assessing systemic zinc for the prevention of OM in patients undergoing HSCT [19] and a case-control study [20]. Both studies showed no efficacy. The LoE was II and no guideline was possible.

Zinc (systemic): Hematologic and solid cancers, CT—prevention

Guideline: No guideline possible (LoE III)

There was a single RCT assessing systemic zinc administration for the prevention of OM in patients receiving CT for solid and hematologic malignancies [21]. This study concluded zinc was ineffective. The LoE was III and no guideline was possible.

Zinc (topical): Hematologic patients, CT—prevention

Guideline: No guideline possible (LoE III)

There was a single RCT assessing topical zinc administration for the prevention of OM in patients receiving CT for leukemia [22]. Zinc sulfate was compounded as a 0.2% mouthwash and the patients were instructed to rinse twice a day for 2 weeks. The topical zinc was compared with 0.2% chlorhexidine mouthwash. The zinc mouthwash was not superior to chlorhexidine mouthwash. The LoE was III and no guideline was possible.

Supersaturated calcium phosphate rinse

Supersaturated calcium phosphate rinses (SCPRs) contain high concentration of calcium and phosphate ions, allowing them to diffuse into the intercellular spaces of the epithelium [23]. The calcium and phosphate ions are hypothesized to play a significant role in inflammatory processes and tissue repair. Table 2 summarizes the details of studies reviewed on SCPR.

Table 2 Studies reported for supersaturated calcium phosphate rinse, 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
SCPR	Topical	Hematol	HSCT	P	Papas 2003 [24]	Y	III	NGP	–	Wasko-Grabowska 2012 [25] – 3 (Y)
					Markiewicz 2012 [27]	Y				Wasko-Grabowska 2011 [26] – 4 (N)
					Svanberg 2015 [28]	N				
	Topical	Hematol and solid	HSCT/CT	T	Raphael 2014 [29]	N	III	NGP	–	
	Topical	H&N	RT-CT	P	Lambrecht 2013 [30]	N	III	NGP		Stokman 2012 [31] – 3 (N)

Non-RCT studies key: 3. non-RCT, 4. cohort, 5. before and after, 6. case-control studies, 7. cross-sectional, 8. case-series, 9. case report, 10. expert opinion

NGP, no guideline possible; SCPR, supersaturated calcium phosphate rinse; *hematol*, hematological; *ca.*, cancer; *P*, prevention; *T*, treatment; *Y*, yes, effective; *N*, no, ineffective; *NGP*, no guideline possible; *RCT*, randomized controlled trials; *HSCT*, hematopoietic stem cell transplant; *CT*, chemotherapy; *H&N*, head and neck

Supersaturated calcium phosphate rinse: HSCT—prevention Guideline: No guideline possible (LoE III)

SCPR administered for the prevention of OM in patients undergoing HSCT was evaluated in 3 RCTs. Of these, 2 RCTs [24, 27] reported that SCPR was effective for the prevention of OM. A single RCT reported that it was ineffective [28]. This latter study compared a combination of SCPR and cryotherapy with cryotherapy alone. This study design may have reduced the risk of OM in both groups. Furthermore, in both study arms, 25% of the patients received reduced-intensity cytotoxic conditioning. These features in the study design might have hindered the SCPR's effect (floor effect).

In addition, 1 comparative study and 1 cohort study have evaluated the efficacy of SCPR in preventing OM in patients undergoing HSCT [25, 26]. A comparison to historic control found that SCPR was effective [25] and the cohort study found it was effective only in a subgroup of patients receiving BEAM (carmustine, etoposide, cytarabine, and melphalan) as a conditioning regimen [26]. An additional study reported using SCPR as part of a multi-agent basic oral care protocol, which did not add information about the effect of SCPR alone [32]. Considering this literature, the LoE is III, and no guideline was possible.

Supersaturated calcium phosphate rinse: HSCT or CT—treatment Guideline: No guideline possible (LoE III)

One RCT evaluated the efficacy of SCPR in treating OM in a heterogenic group of patients including benign hematologic

disorders, malignant hematologic diseases, and solid cancers. The patients were treated with CT as a definitive treatment or as a part of the conditioning regimen for HSCT [29]. No beneficial effect was found for SCPR compared with placebo. The LoE was III and no guideline was possible.

Supersaturated calcium phosphate rinse: RT-CT—prevention Guideline: No guideline possible (LoE III)

For SCPR administered for the treatment of OM in patients receiving RT (with or without CT) for H&N cancer, there was 1 RCT [30] showing no efficacy. There was also 1 comparative study showing ineffectiveness [31]. The LoE was III and no guideline was possible.

Glutamine

Glutamine is the most abundant amino acid in plasma and is a well-known nutrient used to increase cell proliferation as well as survival under metabolic stress conditions [33]. Glutamine is frequently used by rapidly dividing cells. In cancer patients, glutamine deficiency might develop, negatively affecting the function of host tissues [34]. Table 3 summarizes the details of studies reviewed on glutamine.

Glutamine (parenteral): HSCT—prevention Guideline: Recommendation against (LoE I)

The efficacy of parenteral glutamine in the prevention of OM in patients undergoing HSCT was studied in 6 RCTs [35, 37–41]. Of these, there was a single study, conducted in pediatrics, published since the publication of the previous

Table 3 Studies reported for glutamine and elemental diet, 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	Recommendation	Guideline determination	Non-RCT studies
Glutamine	Parenteral	Hematol	HSCT	P	Van Zaanen 1994 [35]	N	I	Recommendation	Parenteral glutamine is not recommended for the prevention of OM in HSCT patients	Kuskonmaz 2008 [36] – 6 (N)	
					Schloerb 1999 [37]	N					
					Pytlík 2002 [38]	N					
					Piccirillo 2003 [39]	Y					
					Bijllevens 2005 [40]	Y					
					Uderzo 2011 [41]^	N					
					Anderson 1998a [42]	Y – auto HSCT / N – allo. HSCT					
					Coghlin 2000 [45]	N					
					Aquino 2005 [46]^	Y					
					Chattopadhyay 2014 [47]	Y					
Elemental diet	PO	H&N	RT-CT	P	Tsujimoto 2015 [48]	Y	II	Suggestion	Oral glutamine at a dose of 10–30 g a day is suggested for the prevention of OM in H&N cancer treated with radiotherapy or radio-chemotherapy. Caution (see text)	Cockerham 2000 [43] – 3 (N) Iyama 2014 [44] – 4 (Y)	
					Huang 2000 [49]	Y					
					Somsuvit 2008 [50]	Y					
					Ward 2009^ [51] – 3 (N)	–					
					Yıldırım 2013 [34] – 4 (N)*	–					
					Skubitz 1996 [53] – 4 (Y)	–					
					Rubio 1998 [54] – 4 (Y)	–					
					Morishita 2016 [58] – 4 (N)	–					
					Anderson 1998b [55]	Y					
					Jebb 1994 [56]	N					
Choi 2007 [57]	Y										
Elemental diet	PO	Hematol	HSCT	P	Peterson 2007 [52]	Y	II	NGP	–	–	
					Anderson 1998b [55]	Y					
					Jebb 1994 [56]	N					
					Choi 2007 [57]	Y					
					–	N					
					–	N					
					–	N					
					–	N					
					–	N					
					–	N					
–	N										

Table 3 (continued)

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline category	Guideline determination	Non-RCT studies
	SS	H&N	RT/RT-CT	P	Tanaka 2016 [59]	Y	IV	NGP	–	Ogata 2016 [60]–4 (Y) Harada 2016 [61]–4 (Y)

Non-RCT studies key: 3, non-RCT; 4, cohort; 5, before and after; 6, case-control studies; 7, cross-sectional; 8, case series; 9, case report; 10, expert opinion

NGP, no guideline possible; RCT, randomized controlled trial; *hematol*, hematological; HSCT, hematopoietic stem cell transplant; CT, chemotherapy; H&N, head and neck; *ca.*, cancer; P, prevention; N, no; ineffective; Y, yes; effective; PO, per os; NGP, no guideline possible; S&S, swish and swallow

*Mix hematologic cancer and solid tumors

^Pediatric patient population

guideline [41]. The glutamine regimens in all studies were comparable. Two RCTs [39, 40] found glutamine to be effective in preventing OM, while the 4 other RCTs [35, 37, 38, 41] did not demonstrate a beneficial effect. Moreover, in 1 RCT [38], a significant statistical correlation of glutamine treatment with relapse ($p = 0.02$) and mortality ($p = 0.05$) was documented [38]. Taking into account the lack of effectiveness in most studies as well as the potential risk, the panel decided to recommend against the use of parenteral glutamine for the prevention of OM in patients undergoing HSCT.

The LoE is I and the recommendation against is in line with the previous guideline about glutamine for this setting.

Glutamine (PO): HSCT—prevention

Guideline: No guideline possible (LoE III)

Three RCTs have evaluated the effectiveness of oral glutamine for the prevention of OM in patients undergoing HSCT [42, 45, 46]. In a single RCT [46], oral glutamine was found to be effective, in another RCT [45], it was ineffective, while the third RCT [42] found it to be effective only in patients who underwent autologous HSCT and ineffective in patients who underwent allogeneic HSCT. In addition, 2 non-RCTs have also reported conflicting results for the efficacy of oral glutamine in preventing OM in this patient population [43, 44]. In light of the above conflicting results, the LoE is III and no guideline was possible.

Glutamine (PO): H&N cancer, RT-CT—prevention

Guideline: Suggestion (LoE II)

Oral glutamine was found to be effective in preventing OM due to RT-CT in H&N cancer patients in 2 RCTs [47, 48]. In one RCT, 10 g of oral glutamine consumed 3 times a day throughout the concomitant RT-CT course, along the 6 weeks of treatment, significantly reduced the severity of OM and its associated pain [48]. In the other RCT, 10 g of oral glutamine given 2 h before RT, beginning at the first RT session and continued all along the RT course, significantly reduced the severity and duration of OM [47]. This study had a heterogeneous patient population, with 65% of the patients to receive RT with concurrent CT, and 35% of the patients receiving RT alone. Therefore, the LoE is II and the panel suggested the use of oral glutamine in H&N cancer patients undergoing RT-CT. The suggestion is with caution due to the higher mortality rate seen in HSCT patients treated with parenteral glutamine [38].

Glutamine (topical): H&N cancer, RT—prevention

Guideline: No guideline possible (LoE III)

A single RCT [49] demonstrated the effectiveness of topical glutamine in preventing OM in H&N cancer patients

undergoing RT. LoE was classified as III. Therefore, it was not possible to provide any guideline.

Glutamine (parenteral): Hematologic malignancies, CT—prevention

Guideline: No guideline possible (LoE III)

A single RCT [50] has evaluated the benefit of parenteral glutamine in preventing OM in 16 AML patients undergoing chemotherapy (8 vs. 8 patients). This study, as well as 2 non-RCTs [34, 51], failed to demonstrate any beneficial effect of glutamine. Accordingly, LoE is III, and no guideline was possible.

Glutamine (PO): Solid cancers, CT—prevention

Guideline: No guideline possible (LoE II)

A RCT in breast cancer patients evaluating a rapid-uptake formulation of glutamine for the prevention of OM reported positive results [52]. Another small RCT in various solid tumors in pediatric and adult patients reported oral glutamine to be effective in the prevention of OM [55]. Two additional cohort studies involving small patient populations ($n = 9$ and $n = 14$) also suggested oral glutamine to be effective [53, 54]. Due to the variability in the glutamine formulation and the patient population, no guideline is possible.

Elemental diet

Elemental diet (ED) formulations have been widely used in Japan for improving nutritional status in patients [61]. These formulas contain amino acids, carbohydrates, vitamins, minerals, and minimal fat and are considered to be a good source of L-glutamine.

Elemental diet (PO): HSCT—prevention

Guideline: No guideline possible (LoE IV)

The use of an ED for the prevention of OM in patients undergoing HSCT was assessed in a single cohort study [58] and found to be ineffective. Therefore, no guideline was possible.

Elemental diet (PO): Solid cancers, CT—prevention

Guideline: No guideline possible (LoE III)

A small RCT [59] tested the efficacy of ED for the prevention of OM in a heterogeneous group of cancer patients treated with chemotherapy. Ten patients were treated with glutamine, 10 patients were treated with both glutamine and ED, and an additional 10 patients received neither glutamine nor ED and served as the control group. The incidence of grade ≥ 2 OM was the highest in the glutamine group, followed by the

control group, and the least in the glutamine plus ED group ($p = 0.04$). ED was found to be effective also in a cohort study of 22 colorectal cancer patients treated with 5-fluorouracil (FU)-based chemotherapy [60].

Elemental diet (PO, swish and swallow): H&N cancer, RT/RT-CT—prevention

Guideline: No guideline possible (LoE IV)

A single retrospective cohort study evaluating the use of ED for the prevention of OM associated with RT (with or without CT) demonstrated that the degree of OM was much lower in patients using ED [61]. Since it was applied as swish and swallow, it is assumed to have both topical and systemic effect.

Vitamin E

Vitamin E refers to eight fat-soluble compounds (α -, β -, γ -, δ -tocopherol, and α -, β -, γ -, δ -tocotrienol) that act as antioxidants. α -Tocopherol, the most common form of vitamin E in human tissues, is considered to have cytoprotective and anti-inflammatory properties [62]. Table 4 summarizes the details of studies reviewed on vitamin E.

Vitamin E (PO, swish and swallow): Hematologic patients, CT—treatment

Guideline: No guideline possible (LoE III)

A single RCT [63] compared the efficacy of swish and swallow vitamin E, pycnogenol, and glycerin (vehicle-control) for the treatment of OM in 72 pediatric patients receiving CT for hematologic malignancies. Both vitamin E and pycnogenol were found to be effective compared with the vehicle ($p < 0.001$ each). However, there was no significant difference between the efficacy observed in the active arms ($p = 0.89$).

Another RCT compared vitamin E tablets to vitamin E oil swish and swallow [67]. There was no control arm in this study. The study recruited 80 children who were undergoing CT for hematological malignancies, 40 in each arm. Vitamin E swish and swallow was superior to vitamin E pills in the treatment of OM ($p < 0.001$).

Vitamin E (topical): Solid cancer, CT—treatment

Guideline: No guideline possible (LoE III)

A single RCT evaluated vitamin E for the treatment of OM in 17 solid cancer patients receiving CT [64]. Vitamin E mouthwash shortened the duration of OM ($p = 0.025$). No other studies in this category were identified. Therefore, no guideline is possible.

Table 4 Studies reported for vitamin E, 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
Vit. E	SS	Hematol [^]	CT	T	Khurana 2013 [63]	Y	III	NGP	–	–
Vit. E	Topical	Solid	CT	T	Wadleigh 1992 [64]	Y	III	NGP	–	–
Vit. E	Topical	Solid [^]	CT	P	Sung 2007 [65]	N	III	NGP	–	–
Vit. E	SS	H&N	RT	P	Ferreira 2004 [66]	Y	II	NGP	–	–

Non-RCT studies key: 3. non-RCT, 4. cohort, 5. before and after, 6. case-control studies, 7. cross-sectional, 8. case series, 9. case report, 10. expert opinion

NGP, no guideline possible; Vit., vitamin; RCT, randomized controlled trial; *hematol*, hematological; CT, chemotherapy; H&N, head and neck; *ca.*, cancer; P, prevention; N, no, ineffective; Y, yes, effective; PO, per os; NGP, no guideline possible; S&S, swish and swallow

[^]Pediatric patient population

Vitamin E (topical): Solid cancers, CT—prevention Guideline: No guideline possible (LoE III)

Topical vitamin E was tested for the prevention of OM in a RCT enrolling 16 pediatric patients treated with CT [65]. It is unclear how many patients were enrolled in each arm as the study reported the sample size in terms of cycles of treatment. Most of these patients were diagnosed with solid cancer. There was no difference between the groups in regard to OM severity.

Vitamin E (swish and swallow): H&N cancer, RT—prevention Guideline: No guideline possible (LoE II)

The efficacy of vitamin E for the prevention of OM in H&N cancer patients treated with RT was tested in a RCT [66]. Vitamin E was applied as a swish and swallow oil. This RCT concluded that vitamin E is effective ($p = 0.038$). No other studies were available in this category. Therefore, no guideline is possible.

Selenium

Selenium is an essential trace element with anti-oxidative and anti-inflammatory properties. It is an important cofactor for glutathione peroxidase, which scavenges free radicals [68]. Table 5 summarizes the details of studies reviewed on selenium.

Selenium (PO): HSCT—prevention Guideline: No guideline possible (LoE III)

The efficacy of oral selenium for the prevention of OM in patients treated with high-dose CT as a part of the conditioning regimen prior to HSCT was evaluated in a single RCT [69]. Selenium was found to be effective in reducing the severity and duration of OM. No other studies on the efficacy of selenium in preventing OM were identified; therefore, no guideline was possible.

Table 5 Studies reported for other vitamins and minerals, 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
selenium	PO	Hematol	HSCT	P	Jahangard 2013 [69]	Y	III	NGP	–	
Folinic	PO/topical	Hematol	HSCT	P				NGP		Sugita 2012 [70] – 4 (Y)
Calcitriol	PO	Hematol [^]	HSCT	P	Hamidieh 2015 [71]	N	II	NGP		

Non-RCT studies key: 3. non-RCT, 4. cohort, 5. before and after, 6. case-control studies, 7. cross-sectional, 8. case series, 9. case report, 10. Expert opinion

NGP, no guideline possible; RCT, randomized controlled trial; *hematol*, hematological; HSCT, hematopoietic stem cell transplantation; *ca.*, cancer; P, prevention; N, no, ineffective; Y, yes, effective; PO, per os; NGP, no guideline possible

[^]Pediatric patient population

Folinic acid

Methotrexate (MTX) is one of the most widely used anti-cancer agents. Folinic acid, also known as leucovorin, is considered to reverse the action of MTX and therefore is usually used in cases of MTX toxicity [72]. Table 5 summarizes the details of studies reviewed on folinic acid.

Folinic acid (PO/topical): HSCT—prevention Guideline: No guideline possible (LoE IV)

Our literature search failed to identify any RCT assessing the efficacy of folinic acid for the prevention of OM in patients undergoing HSCT. A single cohort study [70] found systemic folinic acid to be effective in preventing MTX-induced OM in patients undergoing HSCT ($p = 0.014$). A trend toward efficacy in preventing OM was found for folinic acid mouthwash ($p = 0.051$). Considering the LoE, no guideline was possible.

Calcitriol

Calcitriol, also called 1,25-dihydroxycholecalciferol, is the active metabolite of vitamin D. Vitamin D is a group of fat-soluble hormones responsible for increasing intestinal absorption of calcium, magnesium, and phosphate [73]. Vitamin D is speculated to have anti-inflammatory properties related to its ability to diminish the release of TNF- α and to increase the synthesis of interleukin10 [71]. Table 5 summarizes the details of studies reviewed on calcitriol.

GCalcitriol (PO): HSCT—prevention Guideline: No guideline possible (LoE III)

The use of calcitriol for prevention of OM in patients undergoing HSCT was evaluated in a single RCT [71]. Twenty-eight patients with Fanconi anemia undergoing HSCT were treated with either oral calcitriol or placebo. There was no difference in OM incidence or severity between the two groups.

Discussion

This systematic review is the first part of the update about natural and miscellaneous agents for the management of OM. This part included literature about minerals, vitamins, and supplemental diet. Based on the literature review, several changes have been made to the MASCC/ISOO clinical practice guidelines for the management of OM.

In regard to glutamine, parenteral administration in HSCT patients in order to prevent OM yielded a Recommendation

against its use. This guideline appeared in the previous guidelines [6]; however, the LoE was elevated from II to I due to a new well-designed RCT [41]. A new Suggestion was made for oral glutamine in H&N cancer patients treated with RT-CT for the prevention of OM. This guideline is based on 2 new RCTs [47, 48]. These studies demonstrated that glutamine at a dose range of 10–30 mg/day, delivered throughout the RT-CT, may be effective to prevent OM. This positive guideline for PO glutamine takes into account the negative guideline for parenteral glutamine by attaching a note to this guideline and advising caution due to the higher relapse and mortality rate in parenteral glutamine administration in HSCT patients [38]. It is unclear if the discrepancy between the outcome of parenteral glutamine in HSCT and PO glutamine for RT-CT relies on the mode of administration or on the different underlying diseases and treatment modalities. Of note, in one of the RCTs used to develop this Suggestion, oral glutamine was delivered as a swish-and-swallow [47], and there may be a combined topical and systemic effect in this study.

In regard to zinc, this guideline update reverses the Suggestion made for zinc in the 2014 MASCC/ISOO guidelines for H&N cancer patients treated with RT or RT-CT [4]. This guideline change is based on 2 new RCTs that reported a lack of effectiveness [16, 17]. It is noted that there is an additional new RCT that confirmed the previous RCTs showing positive results with zinc [18]. However, due to the conflicting evidence, it is impossible to conclude a positive effect for zinc.

The publications about zinc used various compounds. The guideline generalized the conclusion because the number of studies was too low to break down the evidence by specific zinc compound. Based on the current evidence, it is impossible to tell if a certain type of zinc is superior compared with other types of zinc in respect of OM prevention. Since the absorption of the zinc is depended on the zinc compound (for example, out of 220-mg zinc sulfate, 50-mg elemental zinc is bioavailable), it is advised to specify in future research the type of zinc compound.

In regard to SCPR, 2 RCTs in patients undergoing HSCT showed some level of effectiveness, while another RCT found that SCPR did not confer any additional benefit in HSCT patients receiving cryotherapy. Evidence from other types of studies was also conflicting. Therefore, the panel concluded that there was conflicting evidence that warrants additional studies prior to instituting a guideline [24, 27, 28].

Other vitamins and minerals for which the literature search identified new studies include vitamin E, selenium, folinic acid, and calcitriol. Due to limited evidence, no guideline was possible for any of these vitamins and minerals. Furthermore, when a combination protocol was studied, the nature of the mixed intervention did not allow a conclusion about any particular component of the combination [74]. While the previous guideline update identified several studies about vitamin A effects on OM [6], no new studies were found on this topic in this review.

Therefore, the status of the previous guideline is unchanged—no guideline possible.

While the timeframe of this literature review ended in mid-2016, several RCTs on the management of OM were published since then. Although not influencing the present guidelines, they are worth mentioning: In a single RCT, oral glutamine has significantly delayed the onset as well as the severity of OM in H&N cancer patients receiving RT-CT [75]. However, glutamine was found to be ineffective in another RCT [76], although it slightly reduced OM compared with placebo. Additionally, a large prospective cohort study has found oral glutamine to be effective in preventing OM [77]. Likewise, a non-blinded RCT in solid cancer patients treated with CT reported that glutamine formulated as sodium azulene sulfonate L-glutamine was effective in preventing OM [78].

Publications post-mid-2016 were also found for ED. A small RCT has evaluated the efficacy of ED in preventing CT-induced OM in esophageal cancer patients [79]. The severity of OM was significantly lower in the ED arm as reported by the patients, but not as measured by the providers. Another RCT failed to demonstrate a beneficial effect of ED in preventing OM in esophageal cancer patient treated with RT with or without concomitant CT [80].

In the search for recently published articles about zinc, a RCT reported that zinc sulfate reduced the incidence and severity of OM in leukemia patients undergoing CT [81]. Additionally, zinc was reported to be effective in 2 comparative studies; one conducted in HSCT and the second conducted in RT for H&N cancer [12, 82].

A search for recently published articles about SCPR identified a large RCT, which concluded that SCPR was ineffective in the management of OM in H&N cancer patients treated with RT/RT-CT [83]. A recent RCT in pediatric patients [84] and comparative studies about SCPR indicated conflicting results about the effectiveness in preventing OM [23, 85].

In summary, for the interventions reviewed in this paper, the available evidence supported guidelines for glutamine. Likewise, based on additional evidence, we reversed a previous guideline for zinc. Considering the growing body of evidence, the guidelines about the agents covered in this section will require updating in the future.

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Compliance with ethical standards

Conflict of interest Per the MASCC Guidelines Policy, employees of commercial entities were not eligible to serve on this MASCC Guidelines Panel.

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Affiliations

Noam Yarom^{1,2}  · Allan Hovan³ · Paolo Bossi⁴ · Anura Ariyawardana^{5,6} · Siri Beier Jensen⁷ · Margherita Gobbo⁸ · Hanan Saca-Hazboun⁹ · Abhishek kandwal¹⁰ · Alessandra Majorana¹¹ · Giulia Ottaviani⁸ · Monica Pentenero¹² · Narmin Mohammed Nasr¹³ · Tanya Rouleau¹⁴ · Anna Skripnik Lucas¹⁵ · Nathaniel Simon Treister^{16,17} · Eyal Zur¹⁸ · Vinisha Ranna¹⁹ · Anusha Vaddi²⁰ · Karis Kin Fong Cheng²¹ · Andrei Barasch²² · Rajesh V. Lalla²³ · Sharon Elad²⁰

¹ Oral Medicine Unit, Sheba Medical Center, Tel Hashomer, Israel

² School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel

³ British Columbia Cancer - Vancouver Centre, Vancouver, Canada

⁴ Medical Oncology, ASST-Spedali Civili, University of Brescia, Brescia, Italy

⁵ College of Medicine and Dentistry, James Cook University, Cairns, Queensland, Australia

⁶ Metro South Oral Health, Queensland Health, Brisbane, Australia

⁷ Department of Dentistry and Oral Health, Faculty of Health, Aarhus University, Aarhus, Denmark

⁸ Division of Oral Medicine and Pathology, Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy

⁹ Al-Maha Cancer foundation, Bethlehem, Palestine

¹⁰ Cancer Research Institute, Himalayan Institute of Medical Sciences, Swami Rama Himayalan University, Dehradun, Uttarakhand, India

¹¹ Department of Medical and Surgical Specialties, Radiological Science and Public Health, Dental School University of Brescia, Brescia, Italy

¹² Department of Oncology, Oral Medicine and Oral Oncology Unit, University of Turin, Turin, Italy

- ¹³ Special Needs Dentistry, Dental Services, Directorate General of Health Services-Muscat Governorate, Ministry of Health, Muscat, Oman
- ¹⁴ Dental Oncology Program, Health Sciences North, North East Cancer Center, Sudbury, ON, Canada
- ¹⁵ Medical Oncology Service, Department of Medicine, NYU Langone Perlmutter Cancer Center, New York, NY, USA
- ¹⁶ Division of Oral Medicine and Dentistry, Brigham and Women's Hospital, Boston, MA, USA
- ¹⁷ Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston, MA, USA
- ¹⁸ Compounding Solutions, Tel-Mond, Israel
- ¹⁹ Department of Oral and Maxillofacial Surgery, The Mount Sinai Hospital, New York, NY 10029, USA
- ²⁰ Oral Medicine, Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY, USA
- ²¹ Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
- ²² Division of Oncology, Weill Cornell Medical College, New York, NY, USA
- ²³ Section of Oral Medicine, University of Connecticut School of Dental Medicine, Farmington, CT, USA