

Systematic review of basic oral care for the management of oral mucositis in cancer patients

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Abstract

Purpose The purpose of this project was to evaluate research in basic oral care interventions to update evidence-based practice guidelines for preventing and treating oral mucositis (OM) in cancer patients undergoing radio- or chemotherapy.

Methods A systematic review of available literature was conducted by the Basic Oral Care Section of the Mucositis Study Group of MASCC/ISOO. Seven interventions—oral care protocols, dental care, normal saline, sodium bicarbonate, mixed medication mouthwash, chlorhexidine, and calcium phosphate—were evaluated using the Hadorn (J Clin Epidemiol 49:749–754, 1996) criteria to determine level of evidence, followed by a guideline determination of one of the following: recommendation, suggestion, or no guideline possible, using Somerfield's (Classic Pap Cur Comments 4:881–886, 2000) schema.

Results Fifty-two published papers were examined by treatment population (radiotherapy, chemotherapy, and hematopoietic

stem cell transplant) and by whether the intervention aimed to prevent or treat OM. The resulting practice suggestions included using oral care protocols for preventing OM across all treatment modalities and age groups and not using chlorhexidine mouthwash for preventing OM in adults with head and neck cancer undergoing radiotherapy. Considering inadequate and/or conflicting evidence, no guidelines for prevention or treatment of OM were possible for the interventions of dental care, normal saline, sodium bicarbonate, mixed medication mouthwash, chlorhexidine in patients receiving chemotherapy or hematopoietic stem cell transplant, or calcium phosphate.

Conclusions The evidence for basic oral care interventions supports the use of oral care protocols in patient populations receiving radiation and/or chemotherapy and does not support chlorhexidine for prevention of mucositis in head and neck cancer patients receiving radiotherapy. Additional well-designed research is needed for other interventions to improve the amount and quality of evidence guiding future clinical care.

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Introduction

Basic oral care, consisting of regularly instituted oral care protocols, dental care before initiation of and during cancer therapy, and the use of bland rinses such as normal saline or sodium bicarbonate, has long been considered the foundation of sound oral hygiene in patients receiving cancer treatment [52]. Although considered important in maintaining oral cleanliness, reducing risk of oral infection, and promoting oral comfort, the evidence for a role in preventing or treating oral mucositis (OM) has been both scarce and inconsistent for basic oral care [52, 54, 58].

The mechanisms through which various basic oral care strategies may directly influence the pathogenesis of OM are unclear, although most have little potential for affecting the complex interplay of molecular factors that lead to mucosal tissue injury [1, 65]. More likely is the possibility that these strategies help promote an oral environment that reduces the potential for, or retards the development of, oral infection that contributes to adverse sequelae of OM [58]. For instance, the regular (scheduled) use of oral care protocols consisting of brushing, flossing, rinsing, and moisturizing, are important in maintaining a clean oral cavity. This practice, in turn, reduces the likelihood of oral infection from normal or abnormal flora, helps minimize trauma-induced mucosal tissue injury, and promotes comfort. The so-called bland oral rinses such as normal saline and sodium bicarbonate have no known active biological properties, yet they contribute to oral hygiene and oral comfort when used within oral care protocols. Mixed medication mouthwashes, commonly consisting of topical coating, anesthetic, and possibly other agents, have little or no direct impact on the pathogenesis of OM. Finally, some of the oral rinses known to have specific biological activity, such as the antimicrobial property of chlorhexidine, do not affect the primary pathways involved in mucositis pathogenesis. Nonetheless, basic oral care is considered a mainstay of supportive care in patients receiving cancer treatment [38, 46, 58].

The first evidence-based clinical practice guidelines for management of mucositis produced by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology, published in 2004 [58], considered basic oral care to be a foundation of care for patients with cancer treatment-induced OM. Few components of basic oral care had sufficient research evidence to formulate guidelines, but despite this lack of evidence, there was general agreement among clinicians from the disciplines of dentistry, dental hygiene, nursing, hematology–oncology, and others that basic oral care was a best practice, dictated by

extensive expert experience and common sense. Similarly, palliation of OM and its associated acute oral pain was also considered a foundation of care, although again evidence was lacking for many interventions, including topical anesthetics and mixtures of various topical agents. Based on evidence available at that time, the specific clinical practice guidelines that resulted from the limited research evidence available included the following:

2004 Guideline: The panel suggests the use of oral care protocols that include patient education in an attempt to reduce the severity of mucositis from chemotherapy or radiotherapy (level of evidence, III; grade of recommendation B).

In addition, the importance of patient, family, and professional healthcare provider education about oral care in patients undergoing cancer treatment is consistently recognized as important [16, 58]. Expanding the body of relevant research to guide development of comprehensive evidence-based practice guidelines for OM was viewed as a way to support such education efforts and to enhance clinical practice [48].

The second version of the evidence-based clinical practice guidelines for management of mucositis from the Mucositis Study Group was an update produced in 2006–2007 and published in comprehensive form in 2007 [38]. The guidelines included research that became available after the 2004 guidelines, but importantly, also presented the concept of “alimentary mucositis,” consisting of oral and gastrointestinal components [36, 37, 55]. The comprehensive guidelines described in Keefe et al. [38] were preceded by a series of individual papers published in *Supportive Care in Cancer* in 2006.

Basic oral care was the subject of one of these papers, describing the work of one of the eight subcommittees functioning within the Mucositis Study Group guidelines panel [46]. The interdisciplinary group (nursing, dentistry, and pediatric dentistry) reviewed literature on basic oral care, bland rinses, oral care protocols and education, and “good clinical practices” such as pain management, oral assessment, oral care, and dental care. The following guidelines resulted from the review:

2007 Guideline: The panel suggests performing basic oral care including a soft toothbrush with regular replacement of the toothbrush (level of evidence IV; grade of recommendation D).

2007 Guideline (updated from 2004): The panel suggests that (oral care) protocol development be interdisciplinary, education should include staff (as well as patients and families), and quality improvement processes should be used to evaluate both protocols and education.

No guidelines were possible for the use of individual bland rinses due to insufficient evidence. However, in the 2007 update, the Basic Oral Care Group formulated conclusions

about the following three areas of “good clinical practice” based on research and clinical literature, clinical practice, and extensive discussion with the full Guidelines Panel;

Pain Management

1. Regular oral pain assessment using validated instruments for self-report is essential.
2. Topical anesthetics or other agents can be considered.

Oral assessment and oral care

1. Initial and ongoing assessment using validated instruments, including patient self-report and professional examination.
2. Preventive oral care regimen.
3. Therapeutic oral care regimen.
4. Regular, systematic oral care hygiene with brushing, flossing, bland rinses, and moisturizer using a standardized oral care protocol.
5. Interdisciplinary approach to oral care (nurse, physician, dentist, dental hygienist, dietician, pharmacist, and others as relevant).

Dental care

1. Dental assessment and dental treatment are important before the start of cancer therapy, for all patients, but especially those with head and neck cancer.
2. Dental professionals should be members of the interdisciplinary health care team throughout active treatment and in follow-up care.

In addition to these two guidelines and good clinical practice recommendations, the Basic Oral Care Group noted that patient and family education should be integrated in all endeavors, and that quality improvement processes should be used to evaluate relevant outcomes. Deployment of these strategies was viewed as essential to patient understanding of and adherence to oral care regimens and appropriate clinical outcome assessment.

The MASCC/ISOO clinical practice guidelines for managing cancer treatment-induced mucositis have recently been thoroughly updated by the Mucositis Study Group Guidelines Panel, yielding a third version [5, 24, 40]. The purpose of the project reported here was to systematically review available literature related to basic oral care and formulate evidence-based guidelines for the use of basic oral care, including oral care protocols, dental care, and various mouthwashes, for preventing and treating OM.

Methods

The Basic Oral Care Section was charged with reviewing research on seven specific interventions: (1) oral care protocols, (2) dental care, (3) normal saline, (4) sodium bicarbonate, (5)

chlorhexidine, (6) mixed medication mouthwash, and (7) calcium phosphate. A literature search for relevant papers indexed in Medline from 1950 to 31 December 2010 was conducted by a research librarian using OVID/MEDLINE and working under the supervision of the Mucositis Study Group chairs (RVL, SE, and JB) [5, 24, 40]. Terms used for the search were generated from previous versions of the guidelines and from current knowledge of the literature and included mucositis, stomatitis, cancer, oral care, oral care protocol, dental care, dental cleaning, oral decontamination, oral hygiene, saline, sodium bicarbonate, baking soda, chlorhexidine, magic/miracle mouthwash, and calcium phosphate. The initial search yielded 129 published papers representing both research and clinical work. The Section Head (DBM) and Co-Head (JSF) independently and then jointly reviewed the entire list, selecting articles for review based on clearly defined inclusion and exclusion criteria. Articles included for review met the criteria of being primary research articles, reflecting a variety of research designs, and having been undertaken to test the effects of various interventions on severity of OM or mucositis-associated symptoms such as oral pain. Review articles, clinical case reports, literature reviews, and other nonresearch articles were excluded from the review. Following this process, 75 papers remained, each of which was assigned to two Section members for a careful review using the Hadorn et al. [33] criteria for assessing flaws and the Somerfield schema [64] for rating levels of evidence. This review process then eliminated an additional 23 papers which did not meet all eligibility criteria, leaving 52 studies that were analyzed for this systematic review.

The detailed methods used by the group and some key considerations were recently published in this journal [5, 24]. In brief, the review process used by seven calibrated reviewers (Section members DBM, JSF, CGB, MEPC, JE, FG, and LO-E) consisted of completion of a structured clinical review form (in standard electronic form) for each paper. This form addressed methodological details, outcomes, major and minor flaws, and a grading schema for level of evidence [33]. As each article was reviewed by two individuals, discrepant ratings occurred and were adjudicated by the Section Head and Co-head using a consensual process after independently reading each article. The seven specific interventions were appraised by treatment population (radiotherapy, chemotherapy, combined therapy, and hematopoietic stem cell transplant) and by the aim of the intervention (prevention or treatment of OM). The Section Head and Co-head determined overall levels of evidence for each type of intervention and formulated draft guidelines based on overall levels of evidence for each intervention. Using the Somerfield criteria [64], they classified guidelines into three types: recommendation, suggestion, or no guideline possible (due to little or no evidence or a lack of consensus on the interpretation of existing evidence). The evidence for each intervention, and

Table 1 Analysis of research on basic oral care components

Name of agent	Route of administration	Cancer type and treatment modality	Indication	Author and year (citation number from reference list) of papers reviewed	Effectiveness	Overall level of evidence	Guideline determination	Comments
Oral care protocols	Topical	CT	P	Beck 1979 [3]	Y	III	The panel suggests the use of oral care protocols to prevent oral mucositis in all age groups and across all treatment modalities. No guideline was possible for the use of oral care protocols in the treatment of oral mucositis in any population because of insufficient and/or conflicting evidence	Beck 1979: tooth brushing, mouthwash (cetylpyridinium chloride), and petroleum jelly for lips Chen et al. 2004: tooth brushing, mouthwash (normal saline), and petroleum jelly for lips Cheng et al. 2001: tooth brushing and mouthwash (sodium chloride solution and 0.2 % chlorhexidine) Cheng et al. 2002: tooth brushing, mouthwash (sodium chloride solution and 0.2 % chlorhexidine) Costa et al. 2003: tooth brushing, mouthwash (0.12 % chlorhexidine vs placebo)
				Chen et al. 2004 [9]	Y			
				Cheng et al. 2001 [12]	Y			
				Cheng et al. 2002 [11]	Y			
				de Brito Costa et al. 2003 [17]	Y			
				Djuric et al. 2006 [19]	Y			Djuric et al. 2006: Intensive dental care+ supervised oral hygiene (toothbrush, mouthwash (0.12%chlorhexidine mixed 3 % hydrogen peroxide & nystatin) vs no prechemotherapy dental care+unsupervised oral hygiene
				Lindquist et al. 1978 [42]	Y			Lindquist et al. 1978: oral hygiene group (pts with no dental plaque vs pts with dental plaque) - mouth wash (tetracycline oral suspension, NVN mouthwash, mycostatin/ xylocaine viscous, cetacaine topical anesthetic sprac, diphenhydramine with kaopectate
				Dodd et al. 1996 [21]	N	IV		Dodd et al. 1996: tooth brushing, flossing, and mouthwash (0.12 % chlorhexidine vs placebo)
				Graham et al. 1993 [32]	Y	III		Graham et al. 1993: tooth brushing and mouthwashes (normal saline)
				Kenny 1990 [39]	Y			Kenny 1990: (1) lip lubricant (nonocclusive preparation of lanolin and aloe vera vs vitamin A and D ointment in a lanolin petrolatum base); (2) oral lubricant (sterile, mint-flavored toothette premoistened with aloe vera and chlorophyll vs 0.9 % sodium chloride solution); (3) cleanser (sterile, mint-flavored toothette premoistened with sodium bicarbonate vs dry, sterile, mint-flavored toothette); and (4) mouthwash (0.9 % sodium bicarbonate solution vs 0.9 % sodium chloride solution)
				Yoneda et al. 2007 [71]	Y			Yoneda et al. 2007: scaling, dental brushing (combination with irrigation and suction)

Table 1 (continued)

Name of agent	Route of administration	Cancer type and treatment modality	Indication	Author and year (citation number from reference list) of papers reviewed	Effectiveness	Overall level of evidence	Guideline determination	Comments
								vs none), and mouthwash (0.5 % povidone-iodine solution)
				Jham et al. 2009 [35]	N			Jham et al. 2009: bethanechol vs artificial saliva
		HSCT with TBI	P	Mori et al. 2008 [50]	Y	III		Mori et al. 2008: mouthwash (ice-cold water) after initiating, during 2 h, and 1 h after cytarabine infusion. The study was not designed to test the effect of cold but to test the effect of local drug removal by mouthrinsing
		HSCT without TBI		Antunes et al. 2010 [2]	N			Antunes et al. 2010: tooth brushing and mouthwash (ethanol-free 0.12 % chlorhexidine vs none)
		HSCT w/wo TBI		Borowski et al. 1994 [6]	Y			Borowski et al. 1994: the intensive oral hygiene care—initial dental treatment, tooth brushing, and mouthwash (chlorhexidine)
				Soga et al. 2011 [63]	Y			Soga et al. 2011: tooth brushing, mouth wash (normal saline/amphotericin B only when fungi were detected), and saliva substitute
				Bhatt et al. 2010 [4]	Y			Bhatt et al. 2010: tooth brushing, cryotherapy, mouthwash depending on mucositis occurrence (chlorhexidine, normal saline, and calcium phosphate rinse magic mouthwash (diphenhydramine, aluminum/magnesium hydroxide, and viscous lidocaine 2 %), and phenol lozenges
				Papas et al. 2003 [53]	Y			Papas et al. 2003: tooth brushing, flossing, and mouthwash (calcium phosphate rinse vs placebo)
		HSCT with TBI	T	Seto et al. 1985 [61]	Y	IV		Seto et al. 1985: tooth brushing, flossing, and mouthwash
		RT	P	Dudjak 1987 [19]	Y	III		Dudjak 1987: tooth brushing, flossing, and mouthwash (half strength hydrogen peroxide vs solution of baking soda and water)
				Janjan et al. 1992 [34]	N			Janjan et al. 1992: daily vs initial and sporadic instruction about oral hygiene (mouthwash - half-strength hydrogen peroxide and salt and soda), nutrition, and analgesic prescriptions
				Shieh et al. 1997 [62]	Y			Shieh et al. 1997: tooth brushing, mouthwash (sterile water), and petroleum jelly for lips (instruction at 1 day vs 1 week before RT vs none)
				Nagy et al. 2007 [51]	N	II		Nagy et al. 2007: enzyme system-based moisturizing gel and toothpaste (both containing glucose oxidase, lactoperoxidase, lysozyme, and lactoferrin vs standard care (carboxymethylcellulose gel and regular fluoride toothpaste)

Table 1 (continued)

Name of agent	Route of administration	Cancer type and treatment modality	Indication	Author and year (citation number from reference list) of papers reviewed	Effectiveness	Overall level of evidence	Guideline determination	Comments
Dental care (administered by a professional)	Topical	RT CT	T P	Dodd et al. 2003 [22] de Morales et al. 2001 [18]	Y N	III III	No guideline was possible for the use of dental care for the prevention or treatment of oral mucositis in any population because of insufficient and/or conflicting evidence	Dodd et al. 2003: tooth brushing, flossing, and mouthwash (sucralfate vs salt and soda) Rojas de Morales et al. 2001: dental preventive protocol–oral physiotherapy, removal of bacterial plaque, mouthwash (0.05 % fluoride), and miconazole oral gel
				Djuric et al. 2006 [19]	Y		No guideline was possible for the use of normal saline mouthwash in the prevention or treatment of oral mucositis in any population because of insufficient and/or conflicting evidence	Djuric et al. 2006: intensive dental care+ supervised oral hygiene (toothbrush and mouthwash (0.12 % chlorhexidine mixed with 3 % hydrogen peroxide and nystatin) vs no prechemotherapy dental care+ unsupervised oral hygiene
Normal saline	Topical	HSCT without TBI CT C/RT	P P P	Melkos et al. 2003 [49] Sorenson et al. 2008 [66] Graham et al. 1993 [32] Kenny 1990 [39] Soga et al. 2010 [63] Epstein et al. 1992 [25] Vokurka et al. 2005 [69] Bhatt et al. 2010 [4] Feber 1996 [26] Maiya et al. 2006 [44]	N N N Y Y N N Y Y N N	IV III IV III III III III III III III III III		Melkos et al. 2003: dental treatment protocol (restoration active carious lesions and extraction of all nonrestorable teeth) vs no dental treatment The panel acknowledged that normal saline is a harmless bland rinse that can be helpful for oral hygiene maintenance and patient comfort
Sodium Bicarbonate rinse	Topical	CT C/RT HSCT without TBI RT	P P T P	Dodd et al. 2000 [20] Kenny 1990 [39] Turhal et al. 2000 [68] Dudjak 1987 [23] Janjan et al. 1992 [34] Maddan et al. 2008 [43] Dodd et al. 2003 [22]	N N Y N Y Y Y Y Y Y Y	III III IV III III III III III III III III III	No guideline was possible for the use of sodium bicarbonate mouthwash for the prevention or treatment of oral mucositis in any population because of insufficient and/or conflicting evidence	The panel acknowledged that sodium bicarbonate is a harmless bland rinse that can be helpful for oral hygiene maintenance and patient comfort

Table 1 (continued)

Name of agent	Route of administration	Cancer type and treatment modality	Indication	Author and year (citation number from reference list) of papers reviewed	Effectiveness	Overall level of evidence	Guideline determination	Comments
Chlorhexidine	Topical	CT	P	Cheng et al. 2002 [11]	Y	III	No guideline was possible for the use of chlorhexidine mouthwash for the prevention or treatment of oral mucositis in patients receiving standard-dose chemotherapy or in HSCT patients because of insufficient and/or conflicting evidence	
				Cheng et al. 2001 [12]	Y		The panel suggests that chlorhexidine mouthwash not be used for the prevention of oral mucositis in head and neck cancer patients receiving radiotherapy	
				de Brito Costa et al. 2003 [17]	Y			
				Sorenson et al. 2008 [66]	Y			
				Cheng 2004 [10]	Y			
				Cheng and Chang 2003 [13]	Y			
				Levy-Polack et al. 1998 [41]	N			
				McGaw and Belch 1985 [45]	Y			
				Pitten et al. 2003 [56]	N			
				Ferretti et al. 1990 [30]	Y			
		CT	T	Cheng et al. 2004 [14]	Y	III		
				Dodd et al. 1996 [21]	N			
		HSCT without TBI	P	Antunes et al. 2010 [2]	N	III		
				Epstein et al. 1992 [25]	N			
				Ferretti et al. 1987 [29]	Y			
				Ferretti et al. 1988 [28]	Y			
				Raether et al. 1989 [57]	N			
				Rutkauskas et al. 1993 [59]	Y			
		HSCT w/wo TBI		Bhatt et al. 2010 [4]	Y			

Table 1 (continued)

Name of agent	Route of administration	Cancer type and treatment modality	Indication	Author and year (citation number from reference list) of papers reviewed	Effectiveness	Overall level of evidence	Guideline determination	Comments
				Borowski et al. 1994 [6]				
		HSCT with TBI	T	Ferretti, et al. 1987 [27]	Y	V		
		RT	P	Madan et al. 2008 [43]	Y	III		
				Footo et al. 1994 [31]	N			
				Samaranyake et al. 1988 [60]	N			
				Spijkervet et al. 1990 [67]	N			
				Weisdorf et al. 1989 [70]	N			
				Cheng & Yuen 2006 [15]	N			
				Ferretti et al. 1990 [30]	N			
Mixed medication mouthwash	Topical	CT	P	Dodd et al. 2000 [20]	N	IV	No guideline was possible for the use of mixed medication mouthwashes for the prevention or treatment of oral mucositis in any population because of insufficient and/or conflicting evidence	Dodd et al. 2000: lidocaine, Benadryl, and Maalox
		C/RT	T	Cerchietti et al. 2003 [8]	N	IV		Cerchietti et al. 2003: A mixture of equal parts of lidocaine, diphenhydramine, and magnesium aluminum hydroxide
		HSCT w/wo TBI	P	Bhatt et al. 2010 [4]	Y	III		Bhatt et al. 2010: tooth brushing, erythrotherapy, mouthwash depending on mucositis occurrence (chlorhexidine, normal saline, calcium phosphate rinse, and magic mouthwash (diphenhydramine, Maalox, and viscous lidocaine 2 %)), and phenol lozenges
Calcium phosphate rinse	Topical	HSCT w/wo TBI	P	Bhatt et al. 2010 [4]	Y	III	No guideline was possible for the use of calcium phosphate rinse for the prevention or treatment of oral mucositis in any population because of insufficient and/or conflicting evidence	Bhatt et al. 2010: Calcium phosphate rinse used in combination with other interventions (described earlier)
				Papas et al. 2003 [53]	Y			

CT chemotherapy, RT radiotherapy, C/RT chemoradiotherapy, HSCT hematopoietic stem cell transplant, w/wo with or without, TBI total body irradiation, P prevention (of mucositis), T treatment (of mucositis), Y yes, N no

the draft guidelines, were discussed at a Guidelines Update Meeting held in Athens, Greece, in 2011. Based on this input, the preliminary guidelines were revised and subsequently finalized for presentation in this paper.

Results

Table 1 presents a detailed description of the 52 articles analyzed by the Basic Oral Care Section, categorized by the seven interventions, and within each intervention by treatment population (i.e., modality) and by indication (prevention or treatment). Overall levels of evidence are shown for each intervention, and a guideline determination is presented, along with comments about individual studies. Results for each intervention are discussed briefly below and should be read in concert with the details shown in Table 1.

Oral care protocols

A relatively large number of studies ($n=24$) were found that tested oral care protocols, although there was significant variation in components of the protocols and many of the studies were older. The vast majority of studies tested effects of oral care protocols on the prevention of OM, whereas only three studies [21, 22, 61] explored effects on treatment of OM. That said, a significant number of the prevention studies continued the use of oral care protocols after OM developed, but remain classified as prevention studies because that was the original indication (or aim of the study). Most of the studies testing oral care protocols for mucositis prevention reported a positive effect across various populations, including children. The overall level of evidence for this intervention was III which, when combined with the consistent evidence from multiple studies, allowed development of the following guideline:

Guideline: The Panel suggests using oral care protocols in the prevention of oral mucositis in all age groups and across all cancer treatment modalities.

No guideline was possible for the use of oral care protocols in the treatment of oral mucositis in any population due to insufficient and/or conflicting evidence.

Dental care

Few studies were found that systematically tested the effects of dental care (administered by a professional) on prevention or treatment of OM. Three studies [18, 19, 49] explored prevention, all using various techniques and agents.

No guideline is possible for the use of dental care in the prevention or treatment of oral mucositis in any population due to insufficient and/or conflicting evidence.

Although there was inadequate evidence to support a guideline related to professional dental care for reducing mucositis severity, the Guidelines Panel agreed that professional dental care is important to the general well-being of patients receiving cancer therapy and, as in previous versions of the guidelines [38, 58] should be considered a foundation of care. In particular, professional pre-treatment evaluation and management of any active oral/dental infection is prudent for patients who are expected to become significantly immunosuppressed because of their cancer therapies. Potential mucosal trauma may lead to mucosal lesions, and as a foundation of care, the management of rough, irregular, or broken dental surfaces and prostheses is important.

Normal saline mouthwash

Nine studies [4, 25, 26, 32, 39, 44, 63, 66, 69] were located that examined the effects of normal saline mouthwash on prevention of OM across a variety of treatment populations. Levels of evidence varied and results were conflicting. Most studies used normal saline in combination with other interventions, and studies using normal saline alone did not show clear benefit.

No guideline is possible for the use of normal saline mouthwash in the prevention or treatment of oral mucositis in any population due to insufficient and/or conflicting evidence.

Despite the lack of evidence, the Guidelines Panel was compelled to make a statement about this agent because it is widely used in clinical settings. Therefore, the Panel acknowledged that normal saline is a harmless bland rinse that can be helpful for oral hygiene maintenance and patient comfort.

Sodium bicarbonate mouthwash

Seven studies were found that studied the effects of sodium bicarbonate mouthwash on prevention [20, 23, 34, 39, 43] or treatment [22, 68] of OM. Levels of evidence varied with conflicting results, and randomized clinical trials showed no clear evidence of benefit.

No guideline is possible for the use of sodium bicarbonate mouthwash in the prevention or treatment of oral mucositis in any population due to insufficient and/or conflicting evidence.

However, as with normal saline, the Guidelines Panel recognized the common use of this agent in clinical practice. Therefore, the Panel acknowledged that sodium bicarbonate is a harmless bland rinse that can be helpful for oral hygiene maintenance and patient comfort. However, sodium bicarbonate may not be as useful in children, who might find it unpleasant or distasteful, and could benefit instead from innocuous rinses such as normal saline, topical anesthetics and parental comforting.

Chlorhexidine mouthwash

Research on the use of chlorhexidine mouthwash in preventing or treating OM spanned more than two decades and interpretation was complex because of conflicting findings, significant variation in study designs, samples, and outcome measures, and incomplete reporting of the components in the mouthwash, particularly alcohol. Twenty-seven studies were found, 24 of which addressed prevention [2, 4, 6, 10–13, 15, 17, 25, 28–31, 41, 43, 45, 56, 57, 59, 60, 66, 67, 70]. The three major cancer treatment populations (chemotherapy, radiation, and hematopoietic stem cell transplant) were well represented, and some studies included children. In most treatment populations, results across multiple studies were conflicting, yielding an overall level of evidence for this intervention of III, with one exception. In patients with head and neck cancer, the evidence demonstrated a lack of effect for prevention of OM. Therefore, the Panel and Section agreed that two separate guideline statements were needed to address the variation in results across treatment populations.

Guideline: The panel suggests that chlorhexidine mouthwash not be used in the prevention of oral mucositis in adult patients with head and neck cancer who are undergoing radiotherapy.

No guideline is possible for the use of chlorhexidine mouthwash in the prevention or treatment of oral mucositis in any other population, due to insufficient and/or conflicting evidence.

However, it is important to note that although chlorhexidine is not indicated for prevention of mucositis, there may be other indications for use, such as the treatment of gingivitis, limited access for plaque control, etc.

Mixed medication mouthwash

Mixed medication mouthwash, comprised of various agents shown in Table 1, is also known by monikers such as “magic mouthwash” and the like. Only three studies were identified that systematically evaluated these mouthwashes, two of which studied prevention [4, 20] and one of which studied treatment of OM [8]. Levels of evidence were IV, III, and IV, respectively, and the results were conflicting.

No guideline is possible for the use of mixed medication mouthwash in the prevention or treatment of oral mucositis in any population due to insufficient and/or conflicting evidence.

Although some clinicians believe that using customized medication mouthwashes can provide comfort, some limitations associated with their use need to be acknowledged. In general, these mouthwashes provide short-lived pain relief and do little to prevent or treat mucositis. The most helpful

agent in these mouthwashes—topical anesthetics—can be easily administered in pure form through other preparations such as viscous lidocaine 2 % or nonviscous topical anesthetics. It should be noted, however, that overuse of lidocaine may suppress the gag reflex in some patients. Mouthwashes that include viscous substances such as milk of magnesia may adhere to the mucous membrane and build up residue, rendering oral care more difficult and uncomfortable. Some of these preparations can contribute to tooth decay because of their sugar content. Finally, these mixtures can become potential sources of infection to immunocompromized patients if stored improperly or contaminated.

Calcium phosphate mouthwash

Two studies were identified that tested supersaturated calcium phosphate mouthwash for preventing OM, both conducted in hematopoietic stem cell transplant patients. Level of evidence was III. In one of these studies (4), the calcium phosphate mouthwash was tested in combination with multiple other interventions (including cryotherapy, chlorhexidine rinse, normal saline, magic mouthwash, and phenol lozenges).

No guideline is possible for the use of calcium phosphate mouthwash in the prevention or treatment of oral mucositis in any population due to insufficient and/or conflicting evidence.

Discussion

The guidelines resulting from this review are little changed from previous versions, with two substantive exceptions. First, chlorhexidine was considered within basic oral care (in contrast to previous versions) because many of the studies also used bland rinses in the experimental and/or control groups. Second, management of oral pain was addressed by a different Section of the Guidelines Panel in this version. In general, the lack of evidence for use of the seven interventions made it difficult to proffer definitive suggestions or recommendations for practice. That said, several interventions which had little supporting evidence but are commonly used in clinical practice were addressed by the Panel in qualifying statements.

The review yielded only two guidelines for practice, one suggesting the use of oral care protocols in the prevention of OM in all age groups and across treatment modalities, and the other suggesting not using chlorhexidine for prevention of OM in head and neck cancer patients receiving radiotherapy. For all other interventions, no formal guidelines were possible, but based on expert consensus opinion, two interventions (normal saline and sodium bicarbonate) were viewed as harmless and, when included in routine oral care practices such as

tooth brushing, may help maintain oral hygiene and promote patient comfort. Another intervention, dental care by professionals, has important positive attributes, in particular the reduction of local infections. A fourth intervention (mixed medication mouthwash) was noted to have some limitations. Use of the two guidelines, and consideration of the qualifying statements related to these four additional interventions, can be expected to result in a modicum of clinical benefit when applied to appropriate patient populations in a systematic manner.

Implementation of the guidelines and related comments in clinical settings can best be undertaken by engaging an interdisciplinary process involving those health care professionals who are most relevant, for example, nursing, dental medicine, medicine, and pharmacy [47, 58]. Such groups can then explore options for building the guidelines and other information resulting from this review into institutional standards of care, algorithms, nursing policies and procedures, or other formulaic approaches to management of OM. The importance of keeping the oral cavity clean, moist, and free of trauma in patients undergoing cancer treatment cannot be over-emphasized. In addition, collaborating best practices with an institutional quality improvement process is essential, beginning with an assessment of status prior to initiation of formalized basic oral care practices, and followed by ongoing monitoring of both positive and negative outcomes [46, 48, 58]. Finally, an essential component of any implementation effort is education of health care professionals, patients, and families [7, 16, 48, 58].

This review has revealed a continuing gap in the available body of research to support the evidence-based use of most of the interventions that were examined. Thus, additional research is clearly needed to generate much-needed evidence to support future clinical practice guidelines. However, practical realities must also be acknowledged. With the exception of commercial products such as chlorhexidine mouthwash and calcium phosphate mouthwash, some of the other interventions (e.g., normal saline and sodium bicarbonate) are routinely used, inexpensive components of basic oral care and oral care protocols in patients undergoing cancer treatment. In a climate of limited fiscal resources for research and emphasis on high value, paradigm-changing interventions, it can be challenging to obtain funding for studies of these commonly used approaches. Thus, given that many of these interventions are low cost, low risk, and already in use, an alternative approach is to employ them in prospective clinical demonstration projects that are initiated under the rubric of quality improvement (QI). A QI approach would, at a minimum, provide baseline data on outcomes and then document improvement in outcomes following systematic use of the selected basic oral care components. Although the resulting evidence would be of a lower level than results obtained through randomized controlled trials, it would nevertheless

be useful in evaluating these routinely used components of basic oral care protocols.

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