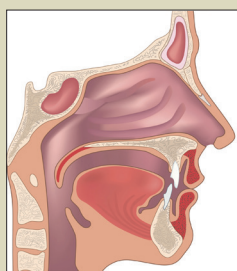


Evidence-Based Interventions for Cancer Treatment–Related Mucositis: Putting Evidence Into Practice

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Mucositis is an inflammatory process that can involve the mucosal epithelial cells from the mouth to the rectum. Historically, mucositis and stomatitis were used interchangeably, but momentum has increased toward more specific terminology since the 2000s. *Stomatitis* refers to inflammatory diseases of the mouth, including the mucosa, dentition, periapices, and periodontium, whereas *mucositis* refers more globally to an inflammatory process involving the mucous membranes of the oral cavity and the gastrointestinal tract. In addition, differentiation is needed regarding mucositis involving the oral cavity and the remainder of the gastrointestinal tract that require use of a scope-type device for close examination. As a result, oral cavity mucositis has been the focus of the majority of the studies reported to date. The mucous membranes beyond the oral cavity are more challenging to view, so the mouth has been presented as revealing potential changes in the gastrointestinal tract. However, because of the variation in morphology, function of different locations, and risks associated with procedures to validate that speculation, evidence is limited. The purpose of this article is to review evidence-based interventions for mucositis, particularly in the oral cavity, and provide clinicians with guidelines for nursing interventions.

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Advances in the pharmacologic and supportive therapy management of cancer treatment-related bone marrow suppression, nausea and vomiting, and neutropenia-related infections have enabled dose escalation of many treatment protocols. However, mucositis is now seen with increased frequency and has evolved into a dose-limiting side effect of treatment. As a result, prevention and management of this side effect have become more relevant for cancer treatment success.

Once believed to involve a simple linear process, mucositis is now seen as a complex process involving many different factors, including the inflammatory process, cellular apoptosis,

cytokines, cytotoxicity of treatments, and micro-organisms in the oral cavity. Sonis (2004) developed a proposed theoretical model to facilitate understanding of the complex process. When the inflammation progresses to a breakdown in the protective mucosal barrier, the micro-organisms normally present in the oral cavity and throughout the gastrointestinal tract are able to enter the bloodstream and cause potentially life-threatening infections that require strategic intervention. In addition to the risk of infections, mucositis causes pain, restricts oral intake, and contributes to malnutrition, interruption of treatment, and increased hospitalizations. The incremental costs of mucositis are usually associated with hospital stays, but

the costs more than double when mucositis is severe (Carlotto, Hogsett, Maiorini, Razulis, & Sonis, 2013).

Patients receiving chemotherapy, epidermal growth factor receptor inhibitors, tyrosine kinase inhibitors, and/or radiation to the head and neck are susceptible to the development of oral mucositis. Mucositis occurs in about 40% of patients after standard doses of chemotherapy, and in as many as 100% of patients receiving high-dose chemotherapy or combination chemotherapy and radiation for head and neck cancer (Gibson et al., 2013). Risks for mucositis include patient- and treatment-related factors (Barasch & Peterson, 2003). Patient-focused factors include poor nutrition, age (children and older adults), neutropenia, poor oral hygiene, genetic factors, impaired salivary function, and use of alcohol and tobacco. Treatment-focused risk factors include specific chemotherapy agents, chemotherapy dose and administration schedule (high doses and stem cell transplantation), combination radiation and chemotherapy, radiation for head and neck cancer, and concomitant medications.

One of the reasons for the wide variation in documented incidence of mucositis is inconsistent use of valid and reliable instruments for the assessment of oral cavity changes. In addition, the severity of mucositis can range from mild erythema

to severe ulcerations and bleeding. Visible changes associated with mucositis include erythema, ulceration, and pseudomembrane formation. Patients with membrane changes experience varying degrees of pain and changes in function including difficulty speaking and swallowing. As a result, patients focus on the symptoms that affect quality of life rather than the risk of life-threatening infection that is of concern to healthcare professionals. The increased length of hospitalization and costs attributed to mucositis are primarily related to pharmacologic management of the infections associated with mucositis and altered ability to maintain oral nutrition. To improve patient outcomes, the goals of nursing care are to prevent membrane breakdown, maintain the ability to eat, and treat or prevent pain.

This article builds on the earlier work by Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP[®]) mucositis teams (Eaton & Tipton, 2009; Harris, Eilers, Harriman, Cashavelly, & Maxwell, 2008; Johnson, Henry, Saca-Hazboun, & Samuel-Blalock, 2014). The span of the work attests to the commitment of oncology nurses to make a difference in patient outcomes through evidence-based practice and the ongoing challenge of mucositis in cancer care.

TABLE 1. Mucositis Interventions: Recommended for Practice

Agent	Findings	Studies Reviewed
Cryotherapy	Topical application: ice water, ice cubes, ice chips, or ice lollipops during chemotherapy infusion Reduced symptoms, incidence, severity, and pain associated with mucositis for patients receiving chemotherapy agents with a short half-life	Aisa et al., 2005; Karagözoglu & Filiz Ulusoy, 2005; Katranci et al., 2012; Kwong, 2004; Lilleby et al., 2006; Migliorati et al., 2006; Mori et al., 2006, 2008; Nikolett et al., 2005; Papadeas et al., 2007; Peterson et al., 2010; Salvador et al., 2012; Svanberg et al., 2010; Vokurka, Bystricka, et al., 2011; Worthington et al., 2011
Low-level laser therapy	Historically has shown mixed results in individual studies in children and adults; however, the majority of recent studies demonstrated a benefit. Systematic reviews showed effectiveness. A meta-analysis showed significant high effect sizes for reducing prevalence, severity, pain, and duration of mucositis. Current European Society for Medical Oncology guidelines recommended low-level laser treatment prior to hematopoietic stem cell transplantation. Most research has been restricted to patients with head and neck cancer and those undergoing transplantation.	Antunes et al., 2008, 2013; Arbabi-Kalati et al., 2013; Arora et al., 2008; Bjordal et al., 2011; Carvalho et al., 2011; Cauwels & Martens, 2011; Clarkson et al., 2010; Cruz et al., 2007; Cunha et al., 2012; de Castro et al., 2013; Figueiredo et al., 2013; Gautam, Fernandes, Vidyasagar, & Maiya, 2012; Gautam, Fernandes, Vidyasagar, Maiya, et al., 2012; Genot-Klastersky et al., 2008; Gouvêa de Lima et al., 2012; Jaguar et al., 2007; Khouri et al., 2009; Kuhn et al., 2009; Lima et al., 2010; Maiya et al., 2006; Migliorati et al., 2006, 2013; Nes & Posso, 2005; Peterson et al., 2010; Qutob et al., 2013; Schubert et al., 2007; Simões et al., 2009; Worthington et al., 2011; Zanin et al., 2010
Oral care protocols	To provide consistent frequent oral hygiene, prophylactic mouth rinses, and routine assessment for early detection Decreased the incidence, duration, and severity of mucositis Structure and components of oral care are important.	Bhatt et al., 2010; Caplinger et al., 2010; Cheng et al., 2001; Dodd et al., 2000; Hogan, 2009; Kwong, 2004; McGuire et al., 2013; Peterson et al., 2011; Qutob et al., 2013; Shih et al., 2002; Yamagata et al., 2012
Palifermin	Effective preventive IV treatment for patients receiving high-dose chemotherapy	Blijlevens et al., 2013; Henke et al., 2011; Langner et al., 2008; Le et al., 2011; Nasilowska-Adamska et al., 2007; Niscola et al., 2009; Peterson et al., 2010; Raber-Durlacher et al., 2013; Rosen et al., 2006; Schmidt et al., 2008; Shea et al., 2007; Sonis, 2009; Spielberger et al., 2004; Stokman et al., 2006; Vadhan-Raj et al., 2010; von Bültz-Ingelöwen et al., 2006
Sodium bicarbonate mouth rinses	Shown to be effective in systematic reviews	Potting et al., 2006; Shih et al., 2002

TABLE 2. Mucositis Interventions: Likely to Be Effective

Agent	Findings	Studies Reviewed
Benzydamine rinses ^a	Rinses have lowered severity and pain of mucositis. A systematic review reported inconsistent results in comparison to chlorhexadine. European Society for Medical Oncology guidelines recommended a benzydamine oral rinse for patients with head and neck cancer. Multinational Association of Supportive Care in Cancer guidelines recommended use in patients with head and neck cancer receiving radiation therapy without chemotherapy.	Epstein et al., 2001, 2008; Kazemian et al., 2009; Kwong, 2004; Nicolatou-Galitis et al., 2013b; Peterson et al., 2011; Petit et al., 2014; Roopashri et al., 2011; Shih et al., 2002
Lactobacillus lozenges	Reduced incidence of oral mucositis compared to placebo in patients with head and neck cancer receiving chemotherapy and radiation therapy	Sharma et al., 2012
Prophylactic chlorhexidine mouth rinses	Reduced incidence and pain associated with oral mucositis in three of five individual studies Two systematic reviews reported moderate support for prophylactic use. Chlorhexidine is not recommended as treatment for existing mucositis.	Cheng et al., 2001, 2004; Dodd et al., 2000; Donnelly et al., 2003; Pitten et al., 2003; Qutob et al., 2013; Sorensen et al., 2008

^a Benzydamine is not approved by the U.S. Food and Drug Administration for use in the United States.

Methods

Search Strategy

The literature search for relevant articles indexed in PubMed and CINAHL[®] was conducted by a research librarian at ONS. Search terms selected were consistent with prior searches for earlier PEP mucositis teams. PubMed was searched for *Mucositis[ti]* OR *Mucositis[majr]* OR “oral complication*” and CINAHL was searched for (MM “Mucositis” OR MM “Stomatitis” OR TI *Mucositis* OR TI *stomatitis* OR “oral complication*”) AND (cancer OR neoplasms OR oncolog* OR chemotherap*). The articles had to include patients with cancer and be published in English from May 1, 2008 to December 31, 2013. The search yielded 635 PubMed citations and 338 CINAHL citations. The abstracts were reviewed based on the following inclusion criteria: (a) studies were full research reports, systematic reviews, guidelines, or meta-analyses; (b) studies had to report on the results of measurement of oral mucositis; (c) studies examined an intervention aimed at affecting the problem of oral mucositis; and (d) the study samples included patients with cancer. Studies were excluded if they included grey literature, were descriptive, or reported intervention effects on the pain of mucositis but not the actual incidence or severity of the symptom mucositis itself. The screening of abstracts identified 138 articles for full article review. After removal of duplicates and studies that did not meet inclusion criteria and the addition of manuscripts retrieved in other topics meeting topic specific criteria, 100 publications were identified for team member review. Four additional studies were identified through an ongoing alert from the ONS research librarian. As a result, 104 publications were added to the prior ONS PEP mucositis work. Because the methods used for the PEP reviews presented in this supplement were consistent across the evidence-based practice teams, the detail of that content is available in Johnson (2014).

Evidence

New research in mucositis is plentiful, particularly related to novel agents with many derived from natural sources. The bulk

of those agents are classified as effectiveness not established because of inadequate research, study design flaws, and conflicting or unconfirmed results. The evidence was challenging to categorize because clinical measurement of mucositis was inconsistent across trials and the validity and reliability of the measurement was not always addressed by the study authors.

Recommended for practice: This category includes interventions for which effectiveness has been demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews and for which expectation of harm is small compared with the benefits. In previous reviews, only oral care protocols were recommended. However, additional therapies now included in this category are cryotherapy, low-level laser therapy, oral care protocols, palifermin, and sodium bicarbonate mouth rinses (see Table 1).

Likely to be effective: These interventions include evidence from a single rigorously conducted controlled trial, consistent evidence from well-designed controlled trials using small samples, evidence from meta-analyses or systematic reviews using small samples, or evidence from guidelines developed from evidence and supported by expert opinion. New recommendations in this category include prophylactic chlorhexidine, benzydamine, and lactobacillus lozenges (see Table 2).

Effectiveness not established: This category includes interventions for which data are insufficient or lack adequate quality. Numerous topical and systemic pharmacologic and nonpharmacologic interventions have been studied for efficacy in the prevention and management of oral mucositis or management of associated pain. Evidence for the interventions is limited because of inconsistent research results, small studies, and study designs. As a result, this category includes the greatest number of agents (see Table 3).

Effectiveness unlikely: These are interventions for which lack of effectiveness has been demonstrated by negative evidence from a single rigorously conducted controlled trial, consistent negative evidence from well-designed controlled trials using small samples, small samples within meta-analysis or systematic reviews, or ineffective guidelines developed by consensus

TABLE 3. Mucositis Interventions: Effectiveness Not Established

Agent	Remarks	Studies Reviewed
Allopurinol mouthwash	Three systematic reviews showed no benefit. One research evidence summary	Kwong, 2004; Panahi et al., 2010; Stokman et al., 2006; Worthington et al., 2004
Aloe vera	One phase II study with patients undergoing RT	Su et al., 2004
Amifostine IV	Seven studies A systematic review showed conflicting results, but associated guidelines suggest use of amifostine.	Antonadou et al., 2002; Buentzel et al., 2006; Gibson et al., 2013; Hwang et al., 2004; Jantunen et al., 2002; Lorusso et al., 2003; Nicolatou-Galitis et al., 2013a; Spencer et al., 2005; Thieblemont et al., 2002
ATL-104	One RCT Plant extract, used as an oral rinse	Hunter et al., 2009
Bethanechol mouth rinse	One systematic review One randomized phase III prospective trial among patients with HNC	Jensen et al., 2013; Jham et al., 2009
Calcium phosphate (Caphosol® mouth rinse)	Two systematic reviews Three small studies in adult patients One small study in pediatric patients	Lambrecht et al., 2013; Markiewicz et al., 2012; Papas et al., 2003; Quinn, 2013; Raphael et al., 2014; Stokman et al., 2012
Calendula officinalis mouthwash	Perennial herb in the daisy family One small RCT	Babae et al., 2013
Camellia and wheat extract tincture or cream	Sinesis leaf extract derived from green tea One small RCT	Carulli et al., 2013
Colchicine mouthwash	Extracted from autumn crocus One RCT	Garavito et al., 2008
Colony-stimulating factors (mouth rinses)	Two systematic reviews A meta-analysis showed possible benefit but weak evidence.	Cawford et al., 1999; Clarkson et al., 2010; Dazzi et al., 2003; Hejna et al., 2001; Hong et al., 2009; Kim et al., 2013; Mantovani et al., 2003; McAleese et al., 2006; Nicolatou-Galitis et al., 2001; Qutob et al., 2013; Rossi et al., 2003; Ryu et al., 2007; Sprinzl et al., 2001; Valcarcel et al., 2002; Worthington et al., 2011; Wu et al., 2009
Epithelial growth factor recombinant epithelial growth factors	Given systemically for prophylaxis Oral spray	
Doxepin mouthwash	Tricyclic antidepressant One open-label study	Epstein et al., 2008
Fluoride chewing gum	One RCT	Gandemer et al., 2007
Flurbiprofen tooth patch	Patch containing 15 mg flurbiprofen One study with historic controls	Stokman et al., 2005
Folinic acid	Given systemically after high-dose methotrexate	Sugita et al., 2012
Glutamine (oral)	Four RCTs One retrospective study	Blijlevens et al., 2005; Cerchiatti et al., 2006; Peterson et al., 2006; Vidal-Casariago et al., 2013; Ward et al., 2009
Hangeshashinto (TA)	A traditional Japanese medicine	Kono et al., 2010
Herbal medicine	A systematic review of 18 studies among patients treated with a single herb	Meyer-Hamme et al., 2013
High-dose laser therapy	Small study in pediatric population	Chermetz et al., 2013
Honey (TA)	Studies included children with low-grade symptoms. Studies in adults showed mixed results and had numerous design limitations.	Abdulrhman et al., 2012; Bardy et al., 2012; Hawley et al., 2014; Jayachandran & Balaji, 2012; Maiti et al., 2012; Motalebnejad et al., 2008; Rashad et al., 2009; Song et al., 2012; Worthington et al., 2011; Yarom et al., 2013
Human intestinal trefoil factor (TA)	Peptide found in mucosal goblet cells One phase II study	Peterson et al., 2009
Hyaluronic acid or sodium hyaluronate oral spray	Mixed small studies and one expert review	Barber et al., 2007; Buchsel & Murphy, 2008; Colella et al., 2010; Vokurka, Skardova, et al., 2011

(Continued on the next page)

TABLE 3. Mucositis Interventions: Effectiveness Not Established (*Continued*)

Agent	Remarks	Studies Reviewed
Indigowood root (gargle)	Chinese herb Small control trial	You et al., 2009
Infrared phototherapy	Use of near infrared wavelength light One study in SCT with melphalan	Hodgson et al., 2011
Irsogladine maleate (oral)	Synthetic drug with antiviral activity One study with patients with HNC	Nomura et al., 2013
Manuka and kanuka (TA)	Plant-derived essential oils with antibacterial, antifungal, anti-inflammatory, and essential analgesic actions Small feasibility study	Maddocks-Jennings et al., 2009
Misoprostol	One review recommended against use in RT for patients with HNC. Two additional studies	Lalla et al., 2012; Nicolatou-Galitis et al., 2013b; Veness et al., 2006
Payayor (herbal medicine)	Small herb cultivated in southeast Asia Used in combination with benzydamine	Jensen et al., 2013; Putwatana et al., 2009
Phenylbutarate mouthwash	Gene modulator approved for urea cycle disorder Small RCT	Yen et al., 2012
Pilocarpine	Cholinergic agonist Two small studies	Awidi et al., 2001; Jensen et al., 2013; Lockhart et al., 2005
Povidone iodine (TA)	Studies with mixed result	Madan et al., 2008; Vokurka et al., 2005; Yoneda et al., 2007
Professional oral care	Two individual studies	Kashiwazaki et al., 2011; Yoneda et al., 2007
Propolis (topical bee glue)	Resin-like material made by bees to coat inside of hive Small pediatric study	Abdulrhman et al., 2012; Tomazevic & Jazbec, 2013
Pycnogenol (topical pine bark extract)	Topical use of pine bark extract Pediatric, single-blind RCT	Khurana et al., 2013
Repifermin (keratinocyte growth factor)	Keratinocyte growth factor 2, administered via IV Small study in SCT	Freytes et al., 2004
Rhodiola algida (herbal solution taken by mouth)	Tibetan plant; Chinese medicine to nourish qi Control trial not specific to mucositis	Loo et al., 2010
Salivary stimulation with a mechanical chewing device	Electrical salivary stimulation Small study in SCT	Jensen et al., 2013; Pimenta Amaral et al., 2012
Samital mouth rinse	Combination of three botanic drug extracts (vaccinium myrtillus, macleaya cordata, and Echinacea angustifolia root) Small control trial	Bertoglio et al., 2013; Pawar et al., 2013
Selenium	One RCT in allogeneic transplantation	Jahangard-Rafsanjani et al., 2013
Tetracaine for pain management	Tetracaine gel combined with other agents Small trial in patients with HNC undergoing RT	Alterio et al., 2006
Triclosan mouth rinses	Antibacterial agent for periodontal therapy Small RCT	Satheeshkumar et al., 2010
Turmeric	One RCT for patients with HNC undergoing RT	Rao et al., 2013
Visible light therapy	Broad band visible light therapy Small RCT in SCT	Elad et al., 2011
Vitamin E (TA)	Two systematic reviews and two studies in pediatric patients	Clarkson et al., 2010; Khurana et al., 2013; Sung et al., 2007; Yarom et al., 2013
Zinc or zinc supplements	One systematic review and seven individual studies	Arbabi-Kalati et al., 2012; Ertekin et al., 2004; Lin et al., 2006, 2010; Mansouri et al., 2011; Mehdipour et al., 2011; Sangthawan et al., 2013; Yarom et al., 2013
HNC—head and neck cancer; RCT—randomized, controlled trial; RT—radiation therapy; SCT—stem cell transplantation; TA—topical application		

or expert opinion. Three agents are in this classification. One of these agents, Traumeel S, consists of multiple homeopathic substances that are expected to have effects on wound healing and inflammation. This compound was studied for its effect on oral mucositis. Other agents previously included and remaining in this category are iseganan and Wobe-Mugos E. Studies with the agents failed to produce statistically significant results (see Table 4). Misoprostol, an agent previously classified in this category, has been moved to effectiveness not established.

Not recommended for practice: Interventions in this category are those for which lack of effectiveness or harmfulness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews or interventions for which the costs, burdens, or harms associated with the intervention exceed anticipated benefit. Two agents remain in this category: chlorhexidine (nonprophylactic) and sucralfate. The concerns with both agents for treatment of mucositis is related to rinse-induced discomfort and taste. The recommendation is supported by other systematic reviews (Kwong, 2004; Shih, Miaskowski, Dodd, Stotts, & MacPhail, 2002; von Bültzingslöwen et al., 2006) (see Table 5).

Other Agents

The extensive volume of literature available regarding treatment and prevention of mucositis presents a challenge for systemic reviews of evidence. In addition to interventions categorized for this article, many others have been trialed and reported in various journals and venues. When systematic reviews are included in a process such as is reported here, multiple agents may have been involved. For the most part, the agents are not included if the researchers concluded that they were not able to make a recommendation. The numerous nonpharmacologic agents used in different settings throughout the world also present a challenge because reviewers were not always able to ascertain the details of the mixtures used. In addition, nonpharmacologic interventions have not always received the same scrutiny prior to use.

Agents that provide a protective barrier are an example of another type of intervention (e.g., Episil®, Gelclair, MuGard™). Typically, that type of agent is regarded as a device, which undergoes a different review process prior to approval for use. As a result, the studies reported may not have the same scientific rigor required for randomized clinical trials. In addition, the literature is not always clear regarding whether the primary

outcome for a given study is pain management or mucositis management.

Implications for Practice

This comprehensive review of mucositis literature examined pharmacologic and nonpharmacologic interventions. Although only a limited number of interventions met the criteria for recommended for practice, they can provide clinicians with a basis for improved outcomes. Nurses are frequently acknowledged as the professionals spending the greatest amount of time with patients. The reality is that nurses in the clinical setting are facing an ever-increasing number of challenges and are expected to do more with less; therefore, nursing interventions such as basic oral care once seen as routine in acute care settings are becoming much less routine. That change in practice and the shift of the majority of cancer care to the outpatient setting have contributed to inconsistency in the promotion of oral care protocols that may be seen as too basic. This review adds support to the use of oral care protocols as the foundation for mucositis prevention and treatment. Nurses have a primary role to relay that importance to patients and families and to provide instruction regarding agents to avoid, particularly those containing alcohol, which has long been stated in the literature. In addition, nurses should recommend the use of sodium bicarbonate mouth rinses as an essential component of the routine oral care protocol.

Although indications for cryotherapy are restricted to potentially mucotoxic agents with a short half-life being administered over a relatively short time period, the intervention is low cost and evidence-based nursing practice. Individuals with cancerous lesions in their oral cavity would not be candidates for the intervention because the vasoconstriction induced by the cooling has the potential to limit exposure of the cancer cells to effective antineoplastic doses. In addition, cryotherapy is not indicated for individuals receiving oxaliplatin because of problems with exposure to cold, including pain, sensitivity, chest tightness, and laryngospasm.

The two remaining recommended interventions fall within interprofessional care. Low-level laser therapy requires the necessary equipment and trained personnel, so it is not available in all treatment centers. Variations in terminology and dose related to the use of lasers and other forms of light therapy for mucositis must be considered. The second intervention, palifermin, has

TABLE 4. Mucositis Interventions: Effectiveness Unlikely

Agent	Findings	Studies Reviewed
Isegran (a peptide)	Did not improve mucositis compared to placebo	Giles et al., 2004; Saunders et al., 2013; Trotti et al., 2004
Traumeel S	Consists of multiple homeopathic substances that are expected to have effects on wound healing and inflammation Showed no benefit in adults or children	Sencer et al., 2012; Steinmann et al., 2012
Wobe-Mugos E	Mixture of proteolytic enzymes Associated with an increase in mucositis incidence and duration in one small study	Dorr & Herrmann, 2007

TABLE 5. Mucositis Interventions: Not Recommended for Practice

Agent	Findings	Studies Reviewed
Chlorhexidine (nonprophylactic)	Did not improve existing mucositis and is not recommended in guidelines or systematic reviews for adults or children	Nashwan, 2011; Niscola et al., 2009; Peterson et al., 2010; Potting et al., 2006; Shih et al., 2002; Worthington et al., 2011
Sucralfate	Did not improve oral mucositis	Castagna et al., 2001; Dodd et al., 2003; Etiz et al., 2000; Nottage et al., 2003; Qutob et al., 2013; Saunders et al., 2013

been approved by the U.S. Food and Drug Administration for patients with hematologic malignancies who receive high doses of chemotherapy and radiation therapy followed by stem cell rescue. Palifermin requires a prescription, and, because of its expense, has not been universally adopted. As a result, further work is needed to identify those to treat with palifermin.

Nurses regularly involved in direct patient care have difficulty staying adequately abreast of the literature on a topic such as mucositis, particularly when their practice is not restricted to the management of one symptom. Therefore, ongoing reviews are at the core to advancing evidence-based practice. Nurses would benefit from ready availability of a simplified version of the tables in the current article to guide practice. With current advances in technology, this could be available electronically and updated regularly. Such a table would also facilitate knowledge regarding the current status of agents that have been identified as unlikely to be effective and/or not recommended for practice. At this time, the number of agents in the categories remains limited, which would facilitate easy review.

Knowledge of resources for accessing the available reports of evidence summaries and how to evaluate new publications will assist nurses in remaining up-to-date regarding changes in the literature. Participation in professional organizations such as ONS and the Multinational Association of Supportive Care in Cancer (MASCC) also provides nurses with support to improve patient outcomes. Initial review of the recommendations from these two organizations may trigger questions regarding inconsistencies. The important component to consider when comparing any other guidelines is to be aware of the criteria used when evaluating individual references and for classification of the levels of evidence once the review content is synthesized. Some of the difference is because ONS is focused on nursing and primarily addresses care in North America, whereas MASCC is multinational and more multidisciplinary in approach. That further explains the stronger focus on dental interventions in the MASCC guidelines as compared to ONS clinical teams, which do not incorporate dental services.

Nurses can contribute to the evidence guiding future practice by participating in research studies. When the resources and opportunities to participate are not available, nurses still can play a key role in improving patient outcomes through performance improvement activities at the local level or perhaps with other institutions. Participation will necessitate the use of valid and reliable assessment tools.

Assessment is the essential initial step for nurses to truly make a difference. Unfortunately, this process is inconsistent at best and often uses instruments that lack essential validity and reliability (see Table 6 in Harris et al., 2008). The more common assessment

instruments, such as the Common Terminology Criteria for Adverse Events, version 4.0 (U.S. Department of Health and Human Services, 2010), and the World Health Organization's (1979) scale, focus on grading mucositis and are used in clinical trials, whereas some instruments, such as the Oral Mucositis Assessment Scale (Sonis et al., 1999), focus on mucous membranes with quantifiable function and objective or subjective measures, and other instruments, such as the Oral Assessment Guide (Eilers, Berger, & Petersen, 1988), address overall changes in the oral cavity but do not grade the mucositis. Awareness of the divergent basis has implications for nursing. Although pain is a common component of the mucositis experience, retaining the pain assessment as a separate element is rational because the rating is dependent on adequacy of treatment, not just the severity of mucositis. Regardless of the mucositis assessment method chosen, the critical aspect involved is that all healthcare providers in an institution should be trained to rate the characteristics in a similar manner and cross-checked to ensure accuracy between assessors.

A baseline assessment is needed to focus on risk factors and the initial status of the oral cavity. Given that one of the identified risk factors for mucositis is cancer treatment, increased understanding is needed about the severity of the risk with a given treatment. Knowing the emetogenicity of cancer treatments, including combination protocols, guides treatment plans, but practice would also benefit from increased awareness of the mucotoxicity of therapies. That information could then enable nursing to establish electronic flags to accompany cancer treatment order sets. The flags could include the need to conduct assessments, which would be followed by evidence-based interventions. Such practice is dependent on adequate evidence that tends to be available, but that will need to be updated regularly.

As is commonly seen in research reports and reviews of evidence, research on mucositis remains limited. The bulk of the literature consists of small studies, nonrandomized designs, and a lack of valid and reliable instruments. Another concern is lack of clarity if the intent of the intervention was prevention or treatment of mucositis. Each concern needs to be addressed with a higher level of science in future work. Although not included in the results section of this review, the population treated and details of the intervention protocol are important to note. Readers are encouraged to refer to the original studies to determine the level of detail available for the studies reported in the current article.

Future Recommendations

The work reported has strengths, particularly in the volume reviewed and the number of nurses involved in the ONS PEP

Patient Education: Mouth Care During Cancer Treatment

The mouth, also called the oral cavity, is often the site of changes from cancer and cancer treatment. These changes can vary from minimal to severe and painful.

One of these changes is called “mucositis” (mu – ko – si – tis). The term *mucositis* means an inflammation of the mucous membranes. It can occur in the mouth and the rest of the gastrointestinal tract. This includes your esophagus, stomach, bowel, and rectum. You may see or feel changes. These changes can include the following.

- Deep or raspy voice: may be like when you have a sore throat or loss of your voice
- Pain when you swallow: may be mild to severe
- Dry or cracked lips: may include bleeding
- Coated and or shiny tongue: may blister or crack
- Altered taste in your mouth and as you eat
- Thick or rope-like saliva and/or loss of saliva
- Reddened tender mouth: may have no sores or open sores with bleeding
- Swollen gums or bleeding

You may have some but not all of these changes. Also, how intense each of the changes is may vary.

What You Can Do to Make a Difference

Care of your mouth is important during cancer treatment. It can help to prevent and treat problems.

Good mouth care includes:

1. Brush your teeth at least two times per day.
 - a. Brush all tooth surfaces for at least 90 seconds using a soft toothbrush.
 - b. Allow your toothbrush to dry before storing.
2. Continue to floss your teeth at least daily. Speak with your nurse if you have not been doing this.
3. Rinse your mouth at least four times per day.
 - a. Use a bland, alcohol-free rinse.
 - b. You may use a mixture of a little salt and baking soda in a cup of warm water for your rinse.

- c. Rinse your mouth more often (every two hours while awake) if you have sores or other problems.

4. Keep your lips moist using a lip moisturizer of your choice. Avoid petroleum-based products or products that cause your lips to burn or feel dry. Select a moisturizing lip balm available “over the counter” through your local pharmacy.
5. Avoid tobacco, alcohol, and irritating foods (hot, rough, acidic, or spicy).

If you develop problems:

- Tell your doctor or nurse.
- Continue to brush your teeth with a soft toothbrush if you can.
- Use a soft foam toothette to clean the entire inside of your mouth. Dip these in the salt and baking soda mixture.
- Take your pain medications as ordered by your doctor.

When to call your doctor or nurse:

- If you have symptoms of an infection such as fever, chills, or white patches in your mouth
- If you develop new or more severe mouth pain
- If you are not able to eat or drink
- Before you go to the dentist or have dental work done

A limited number of other treatments may be available, so check with your doctor or nurse. Always check with them before using any “natural” or other product you can purchase without a specific order.

Note. Full Oncology Nursing Society Putting Evidence Into Practice information for this topic and description of the categories of evidence are located at www.ons.org/practice-resources/pep/mucositis. Users should refer to this resource for full dosages, references, and other essential information about the evidence.

Implications for Practice

- ▶ Assess for oral mucositis with a valid and reliable instrument as an initial step for prevention and management.
- ▶ Develop evidence-based oral care protocols as the foundation for cancer-related mucositis care.
- ▶ Teach oral cavity self-management techniques for mucositis to patients and family members.

review for mucositis. However, improvement is needed. Evidence-based practice encourages nurses to evaluate their processes, which can also guide the PEP process. How can nurses build on past reviews and continue to refine the process used? How should nurses decide when to include miscellaneous agents individually to allow building on the information with future work? How do nurses decide when an intervention that was not found to have adequate evidence should move into an archive rather than remain on an evidence table with an outdated reference? Clinicians need to become critical consumers of attempts to promote the use of specific interventions or new products. Requiring a review of the evidence would serve clinicians and patients. As quality-improvement advocates, clinicians have a responsibility to identify areas of concern and question why established evidence is not being followed. In addition, researchers need to create well-designed studies with valid and reliable instruments, a clear purpose, intervention rigor, and an adequate sample. Finally, those results must be published and shared to pursue excellence as a profession.

Conclusion

Mucositis is a complex process involving the mucosal membranes of the oral cavity. Further knowledge regarding the process will continue to drive the identification of new potential treatments and the reevaluation of others. This update of the evidence for the prevention and management of mucositis provides essential information to guide nursing care of individuals experiencing this potentially life-threatening side effect. The guidelines are not intended to be static in nature, and they should not be blindly followed for every patient. Evidence-based practice must be seen as a process requiring ongoing diligence and review of the literature as well as the appropriateness for application with specific patients. Evidence-based interventions are critical for optimal prevention and management of mucositis. Similarly, the process used for PEP should continually be refined to allow for the provision of meaningful information to clinicians.

References

- Abdulrhman, M., Elbarbary, N.S., Ahmed Amin, D., & Saeid Ebrahim, R. (2012). Honey and a mixture of honey, beeswax, and olive oil-propolis extract in treatment of chemotherapy-induced oral mucositis: A randomized controlled pilot study. *Pediatric Hematology and Oncology*, 29, 285-292. doi:10.3109/08880018.2012.669026
- Aisa, Y., Mori, T., Kudo, M., Yashima, T., Kondo, S., Yokoyama, A., . . . Okamoto, S. (2005). Oral cryotherapy for the prevention of

high-dose melphalan-induced stomatitis in allogeneic hematopoietic stem cell transplant recipients. *Supportive Care in Cancer*, 13, 266-269. doi:10.1007/s00520-004-0726-y

- Alterio, D., Jereczek-Fossa, B.A., Zuccotti, G.F., Leon, M.E., Omodeo Sale, E.O., Pasetti, M., . . . Orecchia, R. (2006). Tetracaine oral gel in patients treated with radiotherapy for head-and-neck cancer: Final results of a phase II study. *International Journal of Radiation Oncology, Biology, Physics*, 64, 392-395. doi:10.1016/j.ijrobp.2005.07.301
- Antonadou, D., Pepelassi, M., Synodinou, M., Puglisi, M., & Throuvalas, N. (2002). Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. *International Journal of Radiation Oncology, Biology, Physics*, 52, 739-747. doi:10.1016/S0360-3016(01)02683-9
- Antunes, H.S., Ferreira, E.M., de Matos, V.D., Pinheiro, C.T., & Ferreira, C.G. (2008). The impact of low power laser in the treatment of conditioning-induced oral mucositis: A report of 11 clinical cases and their review. *Medicina Oral, Patología Oral y Cirugía Bucal*, 13, 189-192.
- Antunes, H.S., Herchenhorn, D., Small, I.A., Araújo, C.M., Viégas, C.M., Cabral, E., . . . Ferreira, C.G. (2013). Phase III trial of low-level laser therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation. *Radiation Therapy and Oncology*, 109, 297-302. doi:10.1016/j.radonc.2013.08.010
- Arbabi-Kalati, F., Arbabi-Kalati, F., Deghatipour, M., & Ansari Moghadam, A. (2012). Evaluation of the efficacy of zinc sulfate in the prevention of chemotherapy-induced mucositis: A double-blind randomized clinical trial. *Archives of Iranian Medicine*, 15, 413-417. doi:012157/AIM.008
- Arbabi-Kalati, F., Arbabi-Kalati, F., & Moridi, T. (2013). Evaluation of the effect of low level laser on prevention of chemotherapy-induced mucositis. *Acta Medica Iranica*, 51, 157-162.
- Arora, H., Pai, K.M., Maiya, A., Vidyasagar, M.S., & Rajeev, A. (2008). Efficacy of He-Ne laser in the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, 105, 180-186. doi:10.1016/j.tripleo.2007.07.043
- Awidi, A., Homsy, U., Kakail, R.I., Mubarak, A., Hassan, A., Kelta, M., . . . El-Alossy, A.S. (2001). Double-blind, placebo-controlled cross-over study of oral pilocarpine for the prevention of chemotherapy-induced oral mucositis in adult patients with cancer. *European Journal of Cancer*, 37, 2010-2014. doi:10.1016/S0959-8049(01)00189-7
- Babae, N., Moslemi, D., Khalilpour, M., Vejdani, F., Moghadamnia, Y., Bijani, A., . . . Moghadamnia, A.A. (2013). Antioxidant capacity of calendula officinalis flowers extract and prevention of radiation induced oropharyngeal mucositis in patients with head and neck cancers: A randomized controlled clinical study. *Daru: Journal of Faculty of Pharmacy, Tebran University of Medical Sciences*, 21, 18. doi:10.1186/2008-2231-21-18
- Barasch, A., & Peterson, D.E. (2003). Risk factors for ulcerative oral mucositis in cancer patients: Unanswered questions. *Oral Oncology*, 39, 91-100. doi:10.1016/S1368-8375(02)00033-7
- Barber, C., Powell, R., Ellis, A., & Hewett, J. (2007). Comparing pain control and ability to eat and drink with standard therapy vs. Gelclair: A preliminary, double centre, randomised controlled trial on patients with radiotherapy-induced oral mucositis. *Supportive Care in Cancer*, 15, 427-440. doi:10.1007/s00520-006-0171-1

- Bardy, J., Molassiotis, A., Ryder, W.D., Mais, K., Sykes, A., Yap, B., . . . Slevin, N. (2012). A double-blind, placebo-controlled, randomised trial of active manuka honey and standard oral care for radiation-induced oral mucositis. *British Journal of Oral and Maxillofacial Surgery*, 50, 221–226. doi:10.1016/j.bjoms.2011.03.005
- Bertoglio, J.C., Calderón, S., Lesina, B., Pilleux, L., Morazzoni, P., Riva, A., . . . Petrangolini, G. (2013). Effect of SAMITAL® in the treatment of chemotherapy-induced mucositis in adult oncohematological patients. *Future Oncology*, 9, 1727–1732. doi:10.2217/fon.13.164
- Bhatt, V., Vendrell, N., Nau, K., Crumb, D., & Roy, V. (2010). Implementation of a standardized protocol for prevention and management of oral mucositis in patients undergoing hematopoietic cell transplantation. *Journal of Oncology Pharmacy Practice*, 16, 195–204. doi:10.1177/1078155209348721
- Bjorndal, J.M., Bensadoun, R.J., Tuner, J., Frigo, L., Gjerde, K., & Lopes-Martins, R.A. (2011). A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. *Supportive Care in Cancer*, 19, 1069–1077. doi:10.1007/s00520-011-1202-0
- Blijlevens, N., de Château, M., Krivan, G., Rabitsch, W., Szomor, A., Pytlik, R., . . . Niederwieser, D. (2013). In a high-dose melphalan setting, palifermin compared with placebo had no effect on oral mucositis or related patient's burden. *Bone Marrow Transplantation*, 48, 966–971. doi:10.1038/bmt.2012.257
- Blijlevens, N.M., Donnelly, J.P., Naber, A.H., Schattenberg, A.V., & DePauw, B.E. (2005). A randomised, double-blinded, placebo-controlled, pilot study of parenteral glutamine for allogeneic stem cell transplant patients. *Supportive Care in Cancer*, 13, 790–796. doi:10.1007/s00520-005-0790-y
- Buchsel, P.C., & Murphy, P.J.M. (2008). Polyvinylpyrrolidone-sodium hyaluronate gel (Gelclair®): A bioadherent oral gel for the treatment of oral mucositis and other painful oral lesions. *Expert Opinion on Drug Metabolism and Toxicology*, 4, 1449–1454. doi:10.1517/17425250802525371
- Buentzel, J., Micke, O., Adamietz, I.A., Monnier, A., Glatzel, M., & deVries, A. (2006). Intravenous amifostine during chemoradiotherapy for head-and-neck cancer: A randomized placebo-controlled phase III study. *International Journal of Radiation Oncology, Biology, Physics*, 64, 684–691. doi:10.1016/j.ijrobp.2005.08.005
- Caplinger, J., Royse, M., & Martens, J. (2010). Implementation of an oral care protocol to promote early detection and management of stomatitis. *Clinical Journal of Oncology Nursing*, 14, 799–802. doi:10.1188/10.CJON.799-802
- Carlotto, A., Hogsett, V.L., Maiorini, E.M., Razulis, J.G., & Sonis, S.T. (2013). The economic burden of toxicities associated with cancer treatment: Review of the literature and analysis of nausea and vomiting, diarrhoea, oral mucositis and fatigue. *Pharmacoeconomics*, 31, 753–766. doi:10.1007/s40273-013-0081-2
- Carulli, G., Rocco, M., Panichi, A., Chios, C.F., Ciurli, E., Mannucci, C., . . . Petrini, M. (2013). Treatment of oral mucositis in hematologic patients undergoing autologous or allogeneic transplantation of peripheral blood stem cells: A prospective, randomized study with a mouthwash containing cameliastensis leaf extract. *Hematology Reports*, 5, 21–25. doi:10.4081/hr.2013.e6
- Carvalho, P.A., Jaguar, G.C., Pellizzon, A.C., Prado, J.D., Lopes, R.N., & Alves, F.A. (2011). Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: A double-blind randomized study in head and neck cancer patients. *Oral Oncology*, 47, 1176–1181. doi:10.1016/j.oraloncology.2011.08.021
- Castagna, L., Benhamou, E., Pedraza, E., Luboinski, M., Forni, M., Brandes, I., . . . Dietrich, P.Y. (2001). Prevention of mucositis in bone marrow transplantation: A double blind randomised controlled trial of sucralfate. *Annals of Oncology*, 12, 953–955. doi:10.1023/A:101119721267
- Cauwels, R.G., & Martens, L.C. (2011). Low level laser therapy in oral mucositis: A pilot study. *European Archives of Paediatric Dentistry*, 12, 118–123. doi:10.1007/BF03262791
- Cawford, J., Tomita, D.K., Mazanet, R., Glaspy, J., & Ozer, H. (1999). Reduction of oral mucositis by filgrastim (r-metHuG-CSF) in patients receiving chemotherapy. *Cytokines, Cellular and Molecular Therapy*, 5, 187–193.
- Cerchiatti, L.C., Navigante, A.H., Lutteral, M.A., Castro, M.A., Kirchuck, R., Bonomi, M., . . . Uchima, P. (2006). Double-blinded, placebo-controlled trial on intravenous L-alanyl-L-glutamine in the incidence of oral mucositis following chemoradiotherapy in patients with head-and-neck cancer. *International Journal of Radiation Oncology, Biology, Physics*, 65, 1330–1337. doi:10.1016/j.ijrobp.2006.03.042
- Chermetz, M., Gobbo, M., Ronfani, L., Ottaviani, G., Zanazzo, G.A., Verzeegnassi, F., . . . Zacchigna, S. (2013). Class IV laser therapy as treatment for chemotherapy-induced oral mucositis in onco-haematological paediatric patients: A prospective study. *International Journal of Paediatric Dentistry*. Advanced online publication. doi:10.1111/ipd.12090
- Cheng, K.K., Chang, A.M., & Yuen, M.P. (2004). Prevention of oral mucositis in pediatric patients treated with chemotherapy: A randomized crossover trial comparing two protocols of oral care. *European Journal of Cancer*, 40, 1208–1216. doi:10.1016/j.ejca.2003.10.023
- Cheng, K.K., Molassiotis, A., Chang, A.M., Wai, W.C., & Cheung, S.S. (2001). Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in pediatric cancer patients. *European Journal of Cancer*, 37, 2056–2063. doi:10.1016/S0959-8049(01)00098-3
- Clarkson, J.E., Worthington, H.V., Furness, S., McCabe, M., Khalid, T., & Meyer, S. (2010). Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database of Systematic Reviews*, 8, CD001973. doi:10.1002/14651858.CD001973.pub4
- Colella, G., Cannavale, R., Vicidomini, A., Rinaldi, G., Compilato, D., & Campisi, G. (2010). Efficacy of a spray compound containing a pool of collagen precursor synthetic aminoacids (l-proline, l-leucine, l-lysine and glycine) combined with sodium hyaluronate to manage chemo/radiotherapy-induced oral mucositis: Preliminary data of an open trial. *International Journal of Immunopathology and Pharmacology*, 23, 143–151.
- Cruz, L.B., Ribeiro, A.S., Rech, A., Rosa, L.G., Castro, C.G., & Brunetto, A.L. (2007). Influence of low-energy laser in the prevention of oral mucositis in children with cancer receiving chemotherapy. *Pediatric Blood and Cancer*, 48, 435–440. doi:10.1002/pbc.20943
- Cunha, C.B., Eduardo, F.P., Zezell, D.M., Bezinelli, L.M., Shitara, P.P., & Correa, L. (2012). Effect of irradiation with red and infrared laser in the treatment of oral mucositis: A pilot study with patients undergoing chemotherapy with 5-FU. *Lasers in Medical Science*, 27, 1233–1240. doi:10.1007/s10103-012-1089-0
- de Castro, J.F., Abreu, E.G., Correia, A.V., Brasil, C.D., da Cruz Perez, D.E., & Pedrosa, F.D. (2013). Low-level laser in prevention and

- treatment of oral mucositis in pediatric patients with acute lymphoblastic leukemia. *Photomedicine and Laser Surgery*, 31, 613–618. doi:10.1089/pho.2012.3327
- Dodd, M.J., Dibble, S.L., Miaskowski, C., MacPhail, L., Greenspan, D., Paul, S.M., . . . Larson, P. (2000). Randomized clinical trial of the effectiveness of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, 90, 39–47. doi:10.1067/moe.2000.105713
- Dodd, M.J., Miaskowski, C., Greenspan, D., MacPhail, L., Shih, A., Shiba, G., . . . Paul, S.M. (2003). Radiation-induced mucositis: A randomized clinical trial of micronized sucralfate versus salt and soda mouthwashes. *Cancer Investigation*, 21, 21–33. doi:10.1081/CNV-120016400
- Donnelly, J.P., Bellm, L.A., Epstein, J.B., Sonis, S.T., & Symonds, R.P. (2003). Antimicrobial therapy to prevent or treat oral mucositis. *Lancet Infectious Diseases*, 3, 405–412. doi:10.1016/S1473-3099(03)00668-6
- Dorr, W., & Herrmann, T. (2007). Efficacy of Wobe-Mugos E for reduction of oral mucositis after radiotherapy: Results of a prospective, randomized, placebo-controlled, triple-blind phase III multicenter study. *Strahlentherapie und Onkologie*, 183, 121–127. doi:10.1007/s00066-007-1634-0
- Eaton, L.H., & Tipton, J.M. (Eds.). (2009). Mucositis. In *Putting Evidence Into Practice: Improving oncology patient outcomes* (pp. 193–213). Pittsburgh, PA: Oncology Nursing Society.
- Eilers, J., Berger, A.M., & Petersen, M.C. (1988). Development, testing, and application of the oral assessment guide. *Oncology Nursing Forum*, 15, 325–330.
- Elad, S., Luboshitz-Shon, N., Cohen, T., Wainchwaig, E., Shapira, M.Y., Resnick, I.B., . . . Or, R. (2011). A randomized controlled trial of visible-light therapy for the prevention of oral mucositis. *Oral Oncology*, 47, 125–130. doi:10.1016/j.oraloncology.2010.11.013
- Epstein, J.B., Epstein, J.D., Epstein, M.S., Oien, H., & Truelove, E.L. (2008). Doxepin rinse for management of mucositis pain in patients with cancer: One week follow-up of topical therapy. *Special Care in Dentistry*, 28, 73–77. doi:10.1111/j.1754-4505.2008.00015.x
- Epstein, J.B., Silverman, S., Paggiarino, D.A., Crockett, S., Schubert, M.M., Senzer, N.N., . . . Leveque, F. G. (2001). Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: Results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Cancer*, 92, 875–885.
- Ertekin, M.V., Koç, M., Karslioglu, I., & Sezen, O. (2004). Zinc sulfate in the prevention of radiation-induced oropharyngeal mucositis: A prospective, placebo-controlled, randomized study. *International Journal of Radiation Oncology, Biology, Physics*, 58, 167–174. doi:10.1016/S0360-3016(03)01562-1
- Etiz, D., Erkal, H.S., Serin, M., Küçük, B., Hepari, A., Elhan, A.H., . . . Cakmak, A. (2000). Clinical and histopathological evaluation of sucralfate in prevention of oral mucositis induced by radiation therapy in patients with head and neck malignancies. *Oral Oncology*, 36, 116–120. doi:10.1016/S1368-8375(99)00075-5
- Figueiredo, A.L., Lins, L., Cattony, A.C., & Falcão, A.F. (2013). Laser therapy in the control of oral mucositis: A meta-analysis. *Revista Da Associacao Medica Brasileira*, 59, 467–474. doi:10.1016/j.ramb.2013.08.003
- Freytes, C.O., Ratanatharathorn, V., Taylor, C., Abboud, C., Chesser, N., Restrepo, A., . . . Odenheimer, D. (2004). Phase I/II randomized trial evaluating the safety and clinical effects of repifermin administered to reduce mucositis in patients undergoing autologous hematopoietic stem cell transplantation. *Clinical Cancer Research*, 10, 8318–8324. doi:10.1158/1078-0432.CCR-04-1118
- Gandemer, V., Le Deley, M.C., Dollfus, C., Auvrignon, A., Bonnaure-Mallet, M., Duval, M., . . . Schmitt, C. (2007). Multicenter randomized trial of chewing gum for preventing oral mucositis in children receiving chemotherapy. *Journal of Pediatric Hematology/Oncology*, 29, 86–94. doi:10.1097/MPH.0b013e318030a3e4
- Garavito, A.A., Cardona, A.F., Reveiz, L., Ospina, E., Yepes, A., & Ospina, V. (2008). Colchicine mouth washings to improve oral mucositis in patients with hematological malignancies: A clinical trial. *Palliative and Supportive Care*, 6, 371–376. doi:10.1017/S147895150800059X
- Gautam, A.P., Fernandes, D.J., Vidyasagar, M.S., Maiya, A.G., & Vadhiraja, B.M. (2012). Low level laser therapy for concurrent chemoradiotherapy induced oral mucositis in head and neck cancer patients: A triple blinded randomized controlled trial. *Radiotherapy and Oncology*, 104, 349–354. doi:10.1016/j.radonc.2012.06.011
- Gautam, A.P., Fernandes, D.J., Vidyasagar, M.S., & Maiya, G.A. (2012). Low level helium neon laser therapy for chemoradiotherapy induced oral mucositis in oral cancer patients: A randomized controlled trial. *Oral Oncology*, 48, 893–897. doi:10.1016/j.oraloncology.2012.03.008
- Genot-Klastersky, M.T., Klastersky, J., Awada, F., Awada, A., Crombez, P., Martinez, M.D., . . . Paesmans, M. (2008). The use of low-energy laser (LEL) for the prevention of chemotherapy- and/or radiotherapy-induced oral mucositis in cancer patients: Results from two prospective studies. *Supportive Care in Cancer*, 16, 1381–1387. doi:10.1007/s00520-008-0439-8
- Gibson, R.J., Keefe, D.M., Lalla, R.V., Bateman, E., Blijlevens, N., Fijlstra, M., . . . Bowen, J.M. (2013). Systematic review of agents for the management of gastrointestinal mucositis in cancer patients. *Supportive Care in Cancer*, 21, 313–326. doi:10.1007/s00520-012-1644-z
- Giles, F.J., Rodriguez, R., Weisdorf, D., Wingard, J.R., Martin, P.J., Fleming, T.R., . . . Hurd, D.D. (2004). A phase III, randomized, double-blind, placebo-controlled study of iseganan for the reduction of stomatitis in patients receiving stomatotoxic chemotherapy. *Leukemia Research*, 28, 559–565. doi:10.1016/j.leukres.2003.10.021
- Gouvêa de Lima, A., Villar, R.C., de Castro, G., Jr., Antequera, R., Gil, E., Rosalmeida, M.C., . . . Snitcovsky, I.M. (2012). Oral mucositis prevention by low-level laser therapy in head-and-neck cancer patients undergoing concurrent chemoradiotherapy: A phase III randomized study. *International Journal of Radiation Oncology, Biology, Physics*, 82, 270–275. doi:10.1016/j.ijrobp.2010.10.012
- Harris, D.J., Eilers, J., Harriman, A., Cashavelly, B.J., & Maxwell, C. (2008). Putting Evidence Into Practice: Evidence-based interventions for the management of oral mucositis. *Clinical Journal of Oncology Nursing*, 12, 141–152. doi:10.1188/08.CJON.141-152
- Hawley, P., Hovan, A., McGahan, C.E., & Saunders, D. (2014). A randomized placebo-controlled trial of manuka honey for radiation-induced oral mucositis. *Supportive Care in Cancer*, 22, 751–761. doi:10.1007/s00520-013-2031-0
- Hejna, M., Köstler, W.J., Raderer, M., Steger, G.G., Brodowicz, T., Scheithauer, W., . . . Zielinski, C.C. (2001). Decrease of duration and symptoms in chemotherapy-induced oral mucositis by topical

- GM-CSF: Results of a prospective randomized trial. *European Journal of Cancer*, 37, 1971–1975. doi:10.1038/sj.bmt.1704521
- Henke, M., Alfonsi, M., Foa, P., Giral, J., Bardet, E., Cerezo, L., . . . Berger, D. (2011). Palifermin decreases severe oral mucositis of patients undergoing postoperative radiochemotherapy for head and neck cancer: A randomized, placebo-controlled trial. *Journal of Clinical Oncology*, 29, 2815–2820. doi:10.1200/JCO.2010.32.4103
- Hodgson, B.D., Margolis, D.M., Salzman, D.E., Eastwood, D., Tarima, S., Williams, L.D., . . . Whelan, H.T. (2011). Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients. *Supportive Care in Cancer*, 20, 1405–1415. doi:10.1007/s00520-011-1223-8
- Hogan, R. (2009). Implementation of an oral care protocol and its effects on oral mucositis. *Journal of Pediatric Oncology Nursing*, 26, 125–135. doi:10.1177/1043454209334356
- Hong, J.P., Lee, S.W., Song, S.Y., Ahn, S.D., Shin, S.S., Choi, E.K., & Kim, J.H. (2009). Recombinant human epidermal growth factor treatment of radiation-induced severe oral mucositis in patients with head and neck malignancies. *European Journal of Cancer Care*, 18, 636–641. doi:10.1111/j.1365-2354.2008.00971.x
- Hunter, A., Mahendra, P., Wilson, K., Fields, P., Cook, G., Peniket, A., . . . Marcus, R. (2009). Treatment of oral mucositis after peripheral blood SCT with ATL-104 mouthwash: Results from a randomized, double-blind, placebo-controlled trial. *Bone Marrow Transplantation*, 43, 563–569. doi:10.1038/bmt.2008.363
- Hwang, W.Y., Koh, L.P., Ng, H.J., Tan, P.H., Chuah, C.T., Fook, S.C., . . . Goh, Y.T. (2004). A randomized trial of amifostine as a cytoprotectant for patients receiving myeloablative therapy for allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, 34, 51–56.
- Jaguar, G.C., Prado, J.D., Nishimoto, I.N., Pinheiro, M.C., de Castro, D.O., Jr., da Cruz Perez, D.E., & Alves, F.A. (2007). Low-energy laser therapy for prevention of oral mucositis in hematopoietic stem cell transplantation. *Oral Diseases*, 13, 538–543. doi:10.1111/j.1601-0825.2006.01330.x
- Jahangard-Rafsanjani, Z., Gholami, K., Hadjibabae, M., Shamshiri, A.R., Alimoghadam, K., Sarayani, A., . . . Ghavamzadeh, A. (2013). The efficacy of selenium in prevention of oral mucositis in patients undergoing hematopoietic SCT: A randomized clinical trial. *Bone Marrow Transplantation*, 48, 832–836. doi:10.1038/bmt.2012.250
- Jantunen, E., Kuittinen, T., & Nousiainen, T. (2002). A pilot study on feasibility and efficacy of amifostine preceding high-dose melphalan with autologous stem cell support in myeloma patients. *Leukemia and Lymphoma*, 43, 1961–1965. doi:10.1080/1042819021000015907
- Jayachandran, S., & Balaji, N. (2012). Evaluating the effectiveness of topical application of natural honey and benzydamine hydrochloride in the management of radiation mucositis. *Indian Journal of Palliative Care*, 18, 190–195. doi:10.4103/0973-1075.105689
- Jensen, S.B., Jarvis, V., Zadik, Y., Barasch, A., Ariyawardana, A., Hovan, A., . . . Elad, S. (2013). Systematic review of miscellaneous agents for the management of oral mucositis in cancer patients. *Supportive Care in Cancer*, 21, 3223–3232. doi:10.1007/s00520-013-1884-6
- Jham, B.C., Chen, H., Carvalho, A.L., & Freire, A.R. (2009). A randomized phase III prospective trial of bethanechol to prevent mucositis, candidiasis, and taste loss in patients with head and neck cancer undergoing radiotherapy: A secondary analysis. *Journal of Oral Science*, 51, 565–572. doi:10.2334/josnusd.51.565
- Johnson, L.A. (2014). Putting Evidence Into Practice: The process for evidence-based research. *Clinical Journal of Oncology Nursing*, 18(Suppl.), 2–4. doi:10.1188/14.CJON.S3.2-4
- Johnson, L.A., Henry, K.S., Saca-Hazboun, H., & Samuel-Blalock, C. (2014). Mucositis. In M. Irwin & L.A. Johnson (Eds.), *Putting Evidence Into Practice: A pocket guide to cancer symptom management* (pp. 159–176). Pittsburgh, PA: Oncology Nursing Society.
- Karagözoglu, S., & Filiz Ulusoy, M.F. (2005). Chemotherapy: The effect of oral cryotherapy on the development of mucositis. *Journal of Clinical Nursing*, 14, 754–765. doi:10.1111/j.1365-2702.2005.01128.x
- Kashiwazaki, H., Matsushita, T., Sugita, J., Shigematsu, A., Kasashi, K., Yamazaki, Y., . . . Inoue, N. (2011). Professional oral health care reduces oral mucositis and febrile neutropenia in patients treated with allogeneic bone marrow transplantation. *Supportive Care in Cancer*, 20, 367–373. doi:10.1007/s00520-011-1116-x
- Katranci, N., Ovayolu, N., Ovayolu, O., & Sevinc, A. (2012). Evaluation of the effect of cryotherapy in preventing oral mucositis associated with chemotherapy: A randomized controlled trial. *European Journal of Oncology Nursing*, 16, 339–344. doi:10.1016/j.ejon.2011.07.008
- Kazemian, A., Kamian, S., Aghili, M., Hashemi, F.A., & Haddad, P. (2009). Benzydamine for prophylaxis of radiation-induced oral mucositis in head and neck cancers: A double-blind placebo-controlled randomized clinical trial. *European Journal of Cancer Care*, 18, 174–178. doi:10.1111/j.1365-2354.2008.00943.x
- Khouri, V.Y., Stracieri, A.B., Rodrigues, M.C., Moraes, D.A., Pieroni, F., Simões, B.P., & Voltarelli, J.C. (2009). Use of therapeutic laser for prevention and treatment of oral mucositis. *Brazilian Dental Journal*, 20, 215–220. doi:10.1590/S0103-64402009000300008
- Khurana, H., Pandey, R.K., Saksena, A.K., & Kumar, A. (2013). An evaluation of vitamin E and pycnogenol in children suffering from oral mucositis during cancer chemotherapy. *Oral Diseases*, 19, 456–464. doi:10.1111/odi.12024
- Kim, K.I., Kim, J.W., Lee, H.J., Kim, B.S., Bang, S.M., Kim, I., . . . Kim, B.K. (2013). Recombinant human epidermal growth factor on oral mucositis induced by intensive chemotherapy with stem cell transplantation. *American Journal of Hematology*, 88, 107–112. doi:10.1002/ajh.23359
- Kono, T., Satomi, M., Chisato, N., Ebisawa, Y., Suno, M., Asama, T., . . . Furukawa, H. (2010). Topical application of hangeshashinto (TJ-14) in the treatment of chemotherapy-induced oral mucositis. *World Journal of Oncology*, 1, 232–235. doi:10.4021/wjon263w
- Kuhn, A., Porto, F.A., Miraglia, P., & Brunetto, A.L. (2009). Low-level infrared laser therapy in chemotherapy-induced oral mucositis: A randomized placebo-controlled trial in children. *Journal of Pediatric Hematology/Oncology*, 31, 33–37. doi:10.1097/MPH.0b013e318192cb8e
- Kwong, K.K. (2004). Prevention and treatment of oropharyngeal mucositis following cancer therapy: Are there new approaches? *Cancer Nursing*, 27, 183–205. doi:10.1097/00002820-200405000-00003
- Lalla, R.V., Gordon, G.B., Schubert, M., Silverman, S., Jr., Hutten, M., Sonis, S.T., . . . Peterson, D.E. (2012). A randomized, double-blind, placebo-controlled trial of misoprostol for oral mucositis secondary to high-dose chemotherapy. *Supportive Care in Cancer*, 20, 1797–1804. doi:10.1007/s00520-011-1277-7
- Lambrecht, M., Mercier, C., Geussens, Y., & Nuyts, S. (2013). The effect of a supersaturated calcium phosphate mouth rinse on the development of oral mucositis in head and neck cancer patients treated with (chemo)radiation: A single-center, randomized,

- prospective study of a calcium phosphate mouth rinse + standard of care versus standard of care. *Supportive Care in Cancer*, 21, 2663–2670. doi:10.1007/s00520-013-1829-0
- Langner, S., Staber, P.B., Schub, N., Gramatzki, M., Grothe, W., Behre, G., . . . Neumeister, P. (2008). Palifermin reduces incidence and severity of oral mucositis in allogeneic stem-cell transplant recipients. *Bone Marrow Transplantation*, 42, 275–279. doi:10.1038/bmt.2008.157
- Le, Q.T., Kim, H.E., Schneider, C.J., Murakozy, G., Skladowski, K., Reinisch, S., . . . Henke, M. (2011). Palifermin reduces severe mucositis in definitive chemoradiotherapy of locally advanced head and neck cancer: A randomized, placebo-controlled study. *Journal of Clinical Oncology*, 29, 2808–2814. doi:10.1200/JCO.2010.32.4095
- Lilleby, K., Garcia, P., Gooley, T., McDonnell, P., Taber, R., Holmberg, L., . . . Bensinger, W. (2006). A prospective, randomized study of cryotherapy during administration of high-dose melphalan to decrease the severity and duration of oral mucositis in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplantation. *Bone Marrow Transplantation*, 37, 1031–1035. doi:10.1038/sj.bmt.1705384
- Lima, A.G., Antequera, R., Gil, E., Peres, M.P., Snitcovsky, I.M., Federucim, M.H., & Villar, R.C. (2010). Efficacy of low level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy induced oral mucositis. *Brazilian Dental Journal*, 21, 186–192.
- Lin, L.C., Que, J., Lin, L.K., & Lin, F.C. (2006). Zinc supplementation to improve mucositis and dermatitis in patients after radiotherapy for head-and-neck cancers: A double-blind, randomized study. *International Journal of Radiation Oncology, Biology, Physics*, 65, 745–750. doi:10.1016/j.ijrobp.2006.01.015
- Lin, Y., Lin, L., Lin, S., & Chang, C. (2010). Discrepancy of the effects of zinc supplementation on the prevention of radiotherapy-induced mucositis between patients with nasopharyngeal carcinoma and those with oral cancers: Subgroup analysis of a double-blind, randomized study. *Nutrition and Cancer*, 62, 682–691. doi:10.1080/01635581003605532
- Lockhart, P.B., Brennan, M.T., Kent, M.L., Packman, C.H., Norton, H.J., Fox, P.C., & Frenette, G. (2005). Randomized controlled trial of pilocarpine hydrochloride for the moderation of oral mucositis during autologous blood stem cell transplantation. *Bone Marrow Transplantation*, 35, 713–720. doi:10.1038/sj.bmt.1704820
- Loo, W.T., Jin, L.J., Chow, L.W., Cheung, M.N., & Wang, M. (2010). Rhodiolaalga improves chemotherapy-induced oral mucositis in breast cancer patients. *Expert Opinion on Investigational Drugs*, 19(Suppl. 1), S91–S100. doi:10.1517/13543781003727057
- Lorusso, D., Ferrandina, G., Greggi, S., Gadducci, A., Pignata, S., Tateo, S., . . . Scambia, G. (2003). Phase III multicenter randomized trial of amifostine as cytoprotectant in first-line chemotherapy in ovarian cancer patients. *Annals of Oncology*, 14, 1086–1093. doi:10.1093/annonc/mdg301
- Madan, P.D., Sequeira, P.S., Shenoy, K., & Shetty, J. (2008). The effect of three mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies: A randomized control trial. *Journal of Cancer Research Therapies*, 4, 3–8. doi:10.4103/0973-1482.39597
- Maddocks-Jennings, W., Wilkinson, J.M., Cavanagh, H.M., & Shillington, D. (2009). Evaluating the effects of the essential oils *Leptospermum scoparium* (manuka) and *Kunzea ericoides* (kanuka) on radiotherapy induced mucositis: A randomized, placebo controlled feasibility study. *European Journal of Oncology Nursing*, 13, 87–93. doi:10.1016/j.ejon.2009.01.002
- Maiti, P.K., Ray, A., Mitra, T.N., Jana, U., Bhattacharya, J., & Ganguly, S. (2012). The effect of honey on mucositis induced by chemoradiation in head and neck cancer. *Journal of the Indian Medical Association*, 110, 453–456.
- Maiya, G., Sagar, M., & Fernandes, D. (2006). Effect of low level helium-neon (He-Ne) laser therapy in the prevention and treatment of radiation induced mucositis in head and neck cancer patients. *Indian Journal of Medical Research*, 124, 399–402.
- Mansouri, A., Hadjibabae, M., Irvani, M., Shamsiri, A.R., Hayatshahi, A., Javadi, M.R., . . . Ghavamzadeh, A. (2011). The effect of zinc sulfate in the prevention of high-dose chemotherapy-induced mucositis: A double-blind, randomized, placebo-controlled study. *Hematological Oncology*, 30, 22–26. doi:10.1002/hon.999
- Mantovani, G., Massa, E., Astara, G., Murgia, V., Gramignano, G., Lusso, M.R., . . . Macciò, A. (2003). Phase II clinical trial of local use of GM-CSF for prevention and treatment of chemotherapy and concomitant chemoradiotherapy-induced severe oral mucositis in advanced head and neck cancer patients: An evaluation of effectiveness, safety and costs. *Oncology Reports*, 10, 197–206.
- Markiewicz, M., Dzierzak-Mietla, M., Frankiewicz, A., Zielinska, P., Koclega, A., Kruszelnicka, M., & Kyrz-Krzemien, S. (2012). Treating oral mucositis with a supersaturated calcium phosphate rinse: Comparison with control in patients undergoing allogeneic hematopoietic stem cell transplantation. *Supportive Care in Cancer*, 20, 2223–2229. doi:10.1007/s00520-012-1489-5
- McAleese, J.J., Bishop, K.M., A'Hern, R., & Henk, J.M. (2006). Randomized phase II study of GM-CSF to reduce mucositis caused by accelerated radiotherapy of laryngeal cancer. *British Journal of Radiology*, 79, 608–613. doi:10.1259/bjr/55190439
- McGuire, D.B., Fulton, J.S., Park, J., Brown, C.G., Correa, M.E.P., Eilers, J., . . . Lalla, R.V. (2013). Systematic review of basic oral care for the management of oral mucositis in cancer patients. *Supportive Care in Cancer*, 21, 3165–3177. doi:10.1007/s00520-013-1942-0
- Mehdipour, M., Taghavi Zenoz, A., Asvadi Kermani, I., & Hosseinpour, A. (2011). A comparison between zinc sulfate and chlorhexidine gluconate mouthwashes in the prevention of chemotherapy-induced oral mucositis. *Daru Journal of Faculty of Pharmacy Tebran University of Medical Sciences*, 19, 71–73.
- Meyer-Hamme, G., Beckmann, K., Radtke, J., Efferth, T., Greten, H.J., Rostock, M., & Schröder, S. (2013). A survey of Chinese medicinal herbal treatment for chemotherapy-induced oral mucositis. *Evidence-Based Complementary and Alternative Medicine*, 2013, 284959. doi:10.1155/2013/284959
- Migliorati, C., Hewson, I., Lalla, R.V., Antunes, H.S., Estilo, C.L., Hodgson, B., . . . Elad, S. (2013). Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients. *Supportive Care in Cancer*, 21, 333–341. doi:10.1007/s00520-012-1605-6
- Migliorati, C.A., Oberle-Edwards, L., & Schubert, M. (2006). The role of alternative and natural agents, cryotherapy and/or laser for management of alimentary mucositis. *Supportive Care in Cancer*, 14, 533–540. doi:10.1007/s00520-006-0049-2
- Mori, T., Hasegawa, K., Okabe, A., Tsujimura, N., Kawata, Y., Yashima, T., . . . Okamoto, S. (2008). Efficacy of mouth rinse in preventing oral mucositis in patients receiving high-dose cytarabine for allogeneic hematopoietic stem cell transplantation. *International Journal of Hematology*, 88, 583–587. doi:10.1007/s12185-008-0181-5

- Mori, T., Yamazaki, R., Aisa, Y., Nakazato, T., Kudo, M., Yashima, T., . . . Okamoto, S. (2006). Brief oral cryotherapy for the prevention of high-dose melphalan-induced stomatitis in allogeneic hematopoietic stem cell transplant recipients. *Supportive Care in Cancer*, 4, 392-395. doi:10.1007/s00520-005-0016-3
- Motallebnejad, M., Akram, S., Moghadamnia, A., Moulana, Z., & Omid, S. (2008). The effect of topical application of pure honey on radiation-induced mucositis: A randomized clinical trial. *Journal of Contemporary Dental Practice*, 9, 40-47.
- Nashwan, A.J. (2011). Use of chlorhexidine mouthwash in children receiving chemotherapy: A review of literature. *Journal of Pediatric Oncology Nursing*, 28, 295-299. doi:10.1177/1043454211408103
- Nasilowska-Adamska, B., Rzepecki, P., Manko, J., Czyz, A., Markiewicz, M., Federowicz, I., . . . Marianska, B. (2007). The influence of palifermin (Kepivance) on oral mucositis and acute graft versus host disease in patients with hematological diseases undergoing hematopoietic stem cell transplant. *Bone Marrow Transplantation*, 40, 983-988. doi:10.1038/sj.bmt.1705846
- Nes, A.G., & Posso, M.B. (2005). Patients with moderate chemotherapy-induced mucositis: Pain therapy using low intensity lasers. *International Nursing Review*, 52, 68-72. doi:10.1111/j.1466-7657.2004.00401.x
- Nicolatou-Galitis, O., Dardoufas, K., Markoulatos, P., Sotiropoulou-Lontou, A., Kyprianou, K., Kolitsi, G., . . . Velegraki, A. (2001). Oral pseudomembranous candidiasis, herpes simplex virus-1 infection, and oral mucositis in head and neck cancer patients receiving radiotherapy and granulocyte-macrophage colony-stimulating factor (GM-CSF) mouthwash. *Journal of Oral Pathology and Medicine*, 30, 471-480. doi:10.1034/j.1600-0714.2001.030008471.x
- Nicolatou-Galitis, O., Sarri, T., Bowen, J., Di Palma, M., Kouloulas, V.E., Niscola, P., . . . Lalla, R.V. (2013a). Systematic review of amifostine for the management of oral mucositis in cancer patients. *Supportive Care in Cancer*, 21, 357-364. doi:10.1007/s00520-012-1613-6
- Nicolatou-Galitis, O., Sarri, T., Bowen, J., Di Palma, M., Kouloulas, V.E., Niscola, P., . . . Lalla, R.V. (2013b). Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients. *Supportive Care in Cancer*, 21, 3179-3189. doi:10.1007/s00520-013-1847-y
- Nikoletti, S., Hyde, S., Shaw, T., Myers, H., & Kristjanson, L.J. (2005). Comparison of plain ice and flavored ice for preventing oral mucositis associated with the use of 5 fluorouracil. *Journal of Clinical Nursing*, 14, 750-753. doi:10.1111/j.1365-2702.2005.01156.x
- Niscola, P., Scaramucci, L., Giovannini, M., Ales, M., Bondanini, F., Cupelli, L., . . . de Fabritiis, P. (2009). Palifermin in the management of mucositis in hematological malignancies: Current evidences and future perspectives. *Cardiovascular and Hematological Agents in Medicinal Chemistry*, 7, 305-312. doi:10.2174/187152509789541873
- Nomura, M., Kamata, M., Kojima, H., Hayashi, K., & Sawada, S. (2013). Irsogladine maleate reduces the incidence of fluorouracil-based chemotherapy-induced oral mucositis. *Annals of Oncology*, 24, 1062-1066. doi:10.1093/annonc/mds584
- Nottage, M., McLachlan, S.A., Brittain, M.A., Oza, A., Hedley, D., Feld, R., . . . Moore, M.J. (2003). Sucralfate mouthwash for prevention and treatment of 5-fluorouracil-induced mucositis: A randomized, placebo-controlled trial. *Supportive Care in Cancer*, 11, 41-47. doi:10.1007/s00520-002-0378-8
- Panahi, Y., Ala, S., Saeedi, M., Okhovatian, A., Bazzaz, N., & Naghizadeh, M. (2010). Allopurinol mouth rinse for prophylaxis of fluorouracil-induced mucositis. *European Journal of Cancer Care*, 19, 308-312. doi:10.1111/j.1365-2354.2008.01042.x
- Papadeas, E., Naxakis, S., Riga, M., & Kalofonos, C. (2007). Prevention of 5-fluorouracil-related stomatitis by oral cryotherapy: A randomized controlled study. *European Journal of Oncology Nursing*, 11, 60-65. doi:10.1016/j.ejon.2006.05.002
- Papas, A.S., Clark, R.E., Martuscelli, G., O'Loughlin, K.T., Johansen, E., & Miller, K.B. (2003). A prospective, randomized trial for the prevention of mucositis in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, 31, 705-712. doi:10.1038/sj.bmt.1703870
- Pawar, D., Neve, R.S., Kalgane, S., Riva, A., Bombardelli, E., Ronchi, M., . . . Morazzoni, P. (2013). SAMITAL® improves chemo/radiotherapy-induced oral mucositis in patients with head and neck cancer: Results of a randomized, placebo-controlled, single-blind Phase II study. *Supportive Care in Cancer*, 21, 827-834. doi:10.1007/s00520-012-1586-5
- Peterson, D.E., Barker, N.P., Akhmadullina, L.I., Rodionova, I., Sherman, N.Z., Davidenko, I.S., . . . Woon, C.W. (2009). Phase II, randomized, double-blind, placebo-controlled study of recombinant human intestinal trefoil factor oral spray for prevention of oral mucositis in patients with colorectal cancer who are receiving fluorouracil-based chemotherapy. *Journal of Clinical Oncology*, 27, 4333-4338. doi:10.1200/JCO.2008.21.2381
- Peterson, D.E., Bensadoun, R.J., Roila, F., & ESMO Guidelines Working Group. (2010). Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. *Annals of Oncology*, 21(Suppl. 5), v261-v265. doi:10.1093/annonc/mdq197
- Peterson, D.E., Bensadoun, R.J., Roila, F., & ESMO Guidelines Working Group. (2011). Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. *Annals of Oncology*, 22(Suppl. 6), vi78-vi84. doi:10.1093/annonc/mdr391
- Peterson, D.E., Jones, J.B., & Petit, R.G., II. (2006). Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. *Cancer*, 109, 322-331. doi:10.1002/cncr.22384
- Petit, L., Sanghera, P., Glaholm, J., & Hartley, A. (2014). The use of MuGard™, Caphosol® and Episil® in patients undergoing chemoradiotherapy for squamous cell carcinoma of the head and neck. *Journal of Radiotherapy in Practice*, 13, 218-225. doi:10.1017/S1460396912000581
- Pimenta Amaral, T.M., Campos, C.C., Moreira dos Santos, T.P., Leles, C.R., Teixeira, A.L., Teixeira, M.M., . . . Silva, T.A. (2012). Effect of salivary stimulation therapies on salivary flow and chemotherapy-induced mucositis: A preliminary study. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, 113, 628-637. doi:10.1016/j.oooo.2011.10.012
- Pitten, F.A., Kiefer, T., Buth, C., Doelken, G., & Kramer, A. (2003). Do cancer patients with chemotherapy-induced leukopenia benefit from an antiseptic chlorhexidine-based oral rinse? A double-blind, block-randomized, controlled study. *Journal of Hospital Infection*, 53, 283-291. doi:10.1053/jhin.2002.1391
- Potting, C.M., Uitterhoeve, R., Op Reimer, W.S., & Van Achterberg, T. (2006). The effectiveness of commonly used mouthwashes for the prevention of chemotherapy-induced oral mucositis: A systematic review. *European Journal of Cancer Care*, 15, 431-439. doi:10.1111/j.1365-2354.2006.00684.x
- Putwatana, P., Sanmanowong, P., Oonprasertpong, L., Junda, T., Pitiporn, S., & Narkwong, L. (2009). Relief of radiation-induced

- oral mucositis in head and neck cancer. *Cancer Nursing*, 32, 82–87. doi:10.1097/01.NCC.0000343362.68129.ed
- Quinn, B. (2013). Efficacy of a supersaturated calcium phosphate oral rinse for the prevention and treatment of oral mucositis in patients receiving high-dose cancer therapy: A review of current data. *European Journal of Cancer Care*, 22, 564–579. doi:10.1111/ecc.12073
- Qutob, A.F., Gue, S., Revesz, T., Logan, R.M., & Keefe, D. (2013). Prevention of oral mucositis in children receiving cancer therapy: A systematic review and evidence-based analysis. *Oral Oncology*, 49, 102–107. doi:10.1016/j.oraloncology.2012.08.008
- Raber-Durlacher, J.E., von Bültzingslöwen, I., Logan, R.M., Bowen, J., Al-Azri, A.R., Everaus, H., . . . Lalla, R.V. (2013). Systematic review of cytokines and growth factors for the management of oral mucositis in cancer patients. *Supportive Care in Cancer*, 21, 343–355. doi:10.1007/s00520-012-1594-5
- Rao, S., Dinkar, C., Vaishnav, L.K., Rao, P., Rai, M.P., Fayad, R., & Baliga, M.S. (2013). The Indian spice turmeric delays and mitigates radiation-induced oral mucositis in patients undergoing treatment for head and neck cancer: An investigational study. *Integrative Cancer Therapies*, 13, 201–210. doi:10.1177/1534735413503549
- Raphael, M.F., den Boer, A.M., Kollen, W.J., Mekelenkamp, H., Abbink, F.C., Kaspers, G.J., . . . Tissing, W.J. (2014). Caphosol, a therapeutic option in case of cancer therapy-induced oral mucositis in children? Results from a prospective multicenter double blind randomized controlled trial. *Supportive Care in Cancer*, 22, 3–6. doi:10.1007/s00520-013-2015-0
- Rashad, U.M., Al-Gezawy, S.M., El-Gezawy, E., & Azzaz, A.N. (2009). Honey as topical prophylaxis against radiochemotherapy-induced mucositis in head and neck cancer. *Journal of Laryngology and Otology*, 123, 223–228. doi:10.1017/S0022215108002478
- Roopashri, G., Jayanthi, K., & Guruprasad, R. (2011). Efficacy of benzydamine hydrochloride, chlorhexidine, and povidone iodine in the treatment of oral mucositis among patients undergoing radiotherapy in head and neck malignancies: A drug trail. *Contemporary Clinical Dentistry*, 2, 8–12. doi:10.4103/0976-237X.79292
- Rosen, L.S., Abdi, E., Davis, I.D., Gutheil, J., Schnell, F.M., Zalberg, J., . . . Clarke, S. (2006). Palifermin reduces the incidence of oral mucositis in patients with metastatic colorectal cancer treated with fluorouracil-based chemotherapy. *Journal of Clinical Oncology*, 24, 5194–5200. doi:10.1200/JCO.2005.04.1152
- Rossi, A., Rosati, G., Colarusso, D., & Manzione, L. (2003). Subcutaneous granulocyte-macrophage colony-stimulating factor in mucositis induced by an adjuvant 5-fluorouracil plus leucovorin regimen. *Oncology*, 64, 353–360. doi:10.1159/000070293
- Ryu, J.K., Swann, S., LeVeque, F., Scarantino, C.W., Johnson, D., Chen, A., . . . Ang, K.K. (2007). The impact of concurrent granulocyte macrophage-colony stimulating factor on radiation-induced mucositis in head and neck cancer patients: A double-blind placebo-controlled prospective phase III study by Radiation Therapy Oncology Group 9901. *International Journal of Radiation Oncology, Biology, Physics*, 67, 643–650.
- Salvador, P., Azusano, C., Wang, L., & Howell, D. (2012). A pilot randomized controlled trial of an oral care intervention to reduce mucositis severity in stem cell transplant patients. *Journal of Pain and Symptom Management*, 44, 64–73. doi:10.1016/j.jpainsymman.2011.08.012
- Sangthawan, D., Phunggrassami, T., & Sinkitjarurnchai, W. (2013). A randomized double-blind, placebo-controlled trial of zinc sulfate supplementation for alleviation of radiation-induced oral mucositis and pharyngitis in head and neck cancer patients. *Journal of the Medical Association of Thailand*, 96, 69–76.
- Satheeshkumar, P.S., Chamba, M.S., Balan, A., Sreelatha, K.T., Bhatathiri, V.N., & Bose, T. (2010). Effectiveness of triclosan in the management of radiation-induced oral mucositis: A randomized clinical trial. *Journal of Cancer Research and Therapeutics*, 6, 466–472. doi:10.4103/0973-1482.77109
- Saunders, D.P., Epstein, J.B., Elad, S., Allemanno, J., Bossi, P., van de Wetering, M.D., . . . Lalla, R.V. (2013). Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients. *Supportive Care in Cancer*, 21, 3191–3207. doi:10.1007/s00520-013-1871-y
- Schmidt, E., Thoennissen, N.H., Rudat, A., Bieker, R., Schliemann, C., Mesters, R.M., . . . Berdel, W.E. (2008). Use of palifermin for the prevention of high-dose methotrexate-induced oral mucositis. *Annals of Oncology*, 19, 1644–1649. doi:10.1093/annonc/mdn179
- Schubert, M.M., Eduardo, F.P., Guthrie, K.A., Franquin, J., Bensadoun, R.J., Migliorati, C.A., . . . Hamdi, M. (2007). A phase III randomized double-blind placebo-controlled clinical trial to determine the efficacy of low level laser therapy for the prevention of oral mucositis in patients undergoing hematopoietic cell transplantation. *Supportive Care in Cancer*, 15, 1145–1154. doi:10.1007/s00520-007-0238-7
- Sencer, S.F., Zhou, T., Freedman, L.S., Ives, J.A., Chen, Z., Wall, D., . . . Oberbaum, M. (2012). Traumeel S in preventing and treating mucositis in young patients undergoing SCT: A report of the Children's Oncology Group. *Bone Marrow Transplantation*, 47, 1409–1414. doi:10.1038/bmt.2012.30
- Sharma, A., Rath, G.K., Chaudhary, S.P., Thakar, A., Mohanti, B.K., & Bahadur, S. (2012). Lactobacillus brevis CD2 lozenges reduce radiation- and chemotherapy-induced mucositis in patients with head and neck cancer: A randomized double-blind placebo-controlled study. *European Journal of Cancer*, 48, 875–881. doi:10.1016/j.ejca.2011.06.010
- Shea, T.C., Kewalramani, T., Mun, Y., Jayne, G., & Dreiling, L.K. (2007). Evaluation of single-dose palifermin to reduce oral mucositis in fractionated total-body irradiation and high-dose chemotherapy with autologous peripheral blood progenitor cell transplantation. *Journal of Supportive Oncology*, 5(Suppl. 2), 60–61.
- Shih, A., Miaskowski, C., Dodd, M.J., Stotts, N.A., & MacPhail, L. (2002). A research review of the current treatments for radiation-induced oral mucositis in patients with head and neck cancer. *Oncology Nursing Forum*, 29, 1063–1078. doi:10.1188/02.ONF.1063-1080
- Simões, A., Eduardo, F.P., Luiz, A.C., Campos, L., Sá, P.H., Cristófar, M., . . . Eduardo, C.P. (2009). Laser phototherapy as topical prophylaxis against head and neck cancer radiotherapy-induced oral mucositis: Comparison between low and high/low power lasers. *Lasers in Surgery and Medicine*, 41, 264–270. doi:10.1002/lsm.20758
- Song, J.J., Twumasi-Ankrah, P., & Salcido, R. (2012). Systematic review and meta-analysis on the use of honey to protect from the effects of radiation-induced oral mucositis. *Advances in Skin and Wound Care*, 25, 23–28. doi:10.1097/01.ASW.0000410687.14363.a3
- Sonis, S.T. (2004). Oral mucositis in cancer therapy. *Journal of Supportive Oncology*, 2(Suppl. 3), 3–8.
- Sonis, S.T. (2009). Efficacy of palifermin (keratinocyte growth

- factor-1) in the amelioration of oral mucositis. *Core Evidence*, 4, 199–205. doi:10.2147/CE.S5995
- Sonis, S.T., Eilers, J.P., Epstein, J.B., LeVegue, F.G., Liggett, W.H., Jr., Mulagha, M.T., . . . Wittes, J.P. (1999). Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. *Cancer*, 85, 2103–2113. doi:10.1002/(SICI)1097-0142(19990515)85:10<2103::AID-CNCR2>3.0.CO;2-0
- Sorensen, J.B., Skovsgaard, T., Bork, E., Damstrup, L., & Ingeberg, S. (2008). Double-blind, placebo-controlled, randomized study of chlorhexidine prophylaxis for 5-fluorouracil-based chemotherapy-induced oral mucositis with nonblinded randomized comparison to oral cooling (cryotherapy) in gastrointestinal malignancies. *Cancer*, 112, 1600–1606. doi:10.1002/cncr.23328
- Spencer, A., Horvath, N., Gibson, J., Prince, H.M., Herrmann, R., Bashrod, J., . . . Taylor, K. (2005). Prospective randomized trial of amifostine cytoprotection in myeloma patients undergoing high-dose melphalan conditioned autologous stem cell transplantation. *Bone Marrow Transplantation*, 35, 971–977. doi:10.1038/sj.bmt.1704946
- Spielberger, R., Stiff, P., Bensinger, W., Gentile, T., Weisdorf, D., Kewalramani, T., . . . Emmanouilides, C. (2004). Palifermin for oral mucositis after intensive therapy for hematologic cancers. *New England Journal of Medicine*, 351, 2590–2598. doi:10.1056/NEJMoa040125
- Sprinzl, G.M., Glava, O., deVries, A., Ulmer, H., Gunkel, A.R., Lukas, P., & Thumfart, W.F. (2001). Local application of granulocyte-macrophage colony stimulating factor (GM-CSF) for the treatment of oral mucositis. *European Journal of Cancer*, 37, 2003–2009. doi:10.1016/S0959-8049(01)00170-8
- Steinmann, D., Eilers, V., Beynenson, D., Buhck, H., & Fink, M. (2012). Effect of Traumeel S on pain and discomfort in radiation-induced oral mucositis: A preliminary observational study. *Alternative Therapies in Health and Medicine*, 18, 12–18.
- Stokman, M.A., Burlage, F.R., & Spijkervet, F.K. (2012). The effect of a calcium phosphate mouth rinse on (chemo) radiation induced oral mucositis in head and neck cancer patients: A prospective study. *International Journal of Dental Hygiene*, 10, 175–180. doi:10.1111/j.1601-5037.2012.00574.x
- Stokman, M.A., Spijkervet, F.K., Boezen, H.M., Schouten, J.P., Roodenburg, J.L., & deVries, E.G. (2006). Preventive intervention possibilities in radiotherapy and chemotherapy-induced oral mucositis: Results of meta-analysis. *Journal of Dental Research*, 85, 690–700. doi:10.1177/154405910608500802
- Stokman, M.A., Spijkervet, F.K., Burlage, F.R., & Roodenburg, J.L. (2005). Clinical effects of flurbiprofen tooth patch on radiation-induced oral mucositis. A pilot study. *Supportive Care in Cancer*, 13, 42–48. doi:10.1007/s00520-004-0674-6
- Su, C.K., Mehta, V., Ravikumar, L., Shah, R., Pinto, H., Halpern, J., . . . Le, Q.T. (2004). Phase II double-blind randomized study comparing oral aloe vera versus placebo to prevent radiation-related mucositis in patients with head-and-neck neoplasms. *International Journal of Radiation Oncology, Biology, Physics*, 60, 171–177. doi:10.1016/j.ijrobp.2004.02.012
- Sugita, J., Matsushita, T., Kashiwazaki, H., Kosugi, M., Takahashi, S., Wakasa, K., . . . Imamura, M. (2012). Efficacy of folinic acid in preventing oral mucositis in allogeneic hematopoietic stem cell transplant patients receiving MTX as prophylaxis for GVHD. *Bone Marrow Transplantation*, 47, 258–264. doi:10.1038/bmt.2011.53
- Sung, L., Tomlinson, G.A., Greenberg, M.L., Koren, G., Judd, P., Ota, S., & Feldman, B.M. (2007). Serial controlled N-of-1 trials of topical vitamin E as prophylaxis for chemotherapy-induced oral mucositis in paediatric patients. *European Journal of Cancer*, 43, 1269–1275. doi:10.1016/j.ejca.2007.02.001
- Svanberg, A., Öhrn, K., & Birgegård, G. (2010). Oral cryotherapy reduces mucositis and improves nutrition A randomised controlled trial. *Journal of Clinical Nursing*, 19, 2146–2151. doi:10.1111/j.1365-2702.2010.03255.x
- Thieblemont, V.C., Dumontet, C., Saad, H., Roch, N., Bouafia, F., Arnaud, P., . . . Coiffier, B. (2002). Amifostine reduces mucosal damage after high-dose melphalan conditioning and autologous peripheral blood progenitor cell transplantation for patients with multiple myeloma. *Bone Marrow Transplantation*, 30, 769–775. doi:10.1038/sj.bmt.1703757
- Tomazevic, T., & Jazbec, J. (2013). A double blind randomised placebo controlled study of propolis (bee glue) effectiveness in the treatment of severe oral mucositis in chemotherapy treated children. *Complementary Therapies in Medicine*, 21, 306–312. doi:10.1016/j.ctim.2013.04.002
- Trotti, A., Garden, A., Warde, P., Symonds, P., Langer, C., Redman, R., . . . Ang, K.K. (2004). A multinational, randomized phase III trial of isegagan HCl oral solution for reducing the severity of oral mucositis in patients receiving radiotherapy for head-and-neck malignancy. *International Journal of Radiation Oncology, Biology, Physics*, 58, 674–681. doi:10.1016/S0360-3016(03)01627-4
- U.S. Department of Health and Human Services. (2010). *Common Terminology Criteria for Adverse Events (CTCAE)* [v4.0]. Retrieved from <http://1.usa.gov/1wHuEAY>
- Vadhan-Raj, S., Trent, J., Patel, S., Zhou, X., Johnson, M.M., Araujo, D., . . . Benjamin, R.S. (2010). Single-dose palifermin prevents severe oral mucositis during multicycle chemotherapy in patients with cancer: A randomized trial. *Annals of Internal Medicine*, 153, 358–367. doi:10.1059/0003-4819-153-6-201009210-00003
- Valcarcel, D., Sanz, M.A., Sureda, A., Sala, M., Munoz, L., Subira, M., . . . Sierra, J. (2002). Mouth-washings with recombinant human granulocyte-macrophage colony stimulation factor (rhGM-CSF) do not improve grade III-IV oropharyngeal mucositis (OM) in patients with hematological malignancies undergoing stem cell transplantation. Results of a randomized, double-blind, placebo-controlled study. *Bone Marrow Transplantation*, 29, 783–787. doi:10.1038/sj.bmt.1703543
- Veness, M.J., Foroudi, F., Gebiski, V., Timms, I., Sathiyaseelan, Y., Cakir, B., & Tiver, K.W. (2006). Use of topical misoprostol to reduce radiation-induced mucositis: Results of a randomized, double-blind, placebo-controlled trial. *Australasian Radiology*, 50, 468–474. doi:10.1111/j.1440-1673.2006.01628.x
- Vidal-Casariago, A., Calleja-Fernandez, A., Ballesteros-Pomar, M.D., & Cano-Rodriguez, I. (2013). Efficacy of glutamine in the prevention of oral mucositis and acute radiation-induced esophagitis: A retrospective study. *Nutrition and Cancer*, 65, 424–429. doi:10.1080/01635581.2013.765017
- Vokurka, S., Bystricka, E., Koza, V., Scudlova, J., Pavlicova, V., Valentova, D., . . . Misaniova, L. (2005). The comparative effects of povidone-iodine and normal saline mouthwashes on oral mucositis in patients after high-dose chemotherapy and APB-SCT—Results of a randomized multicentre study. *Supportive Care in Cancer*, 13, 554–558. doi:10.1007/s00520-005-0792-9
- Vokurka, S., Bystricka, E., Scudlova, J., Mazur, E., Visokaiova, M., Vasilieva, E., . . . Streinerova, K. (2011). The risk factors for oral mucositis and the effect of cryotherapy in patients after the BEAM and HD-I-PAM 200 mg/m² autologous hematopoietic stem

- cell transplantation. *European Journal of Oncology Nursing*, 15, 508–512. doi:10.1016/j.ejon.2011.01.006
- Vokurka, S., Skardova, J., Hruskova, R., Kabatova-Maxova, K., Svoboda, T., Bystricka, E., . . . Koza, V. (2011). The effect of polyvinylpyrrolidone-sodium hyaluronate gel (Gelclair) on oral microbial colonization and pain control compared with other rinsing solutions in patients with oral mucositis after allogeneic stem cells transplantation. *Medical Science Monitor*, 17, CR572–CR576. doi:10.12659/MSM.881983
- von Bültzingslöwen, I., Brennan, M.T., Spijkervet, F.K., Logan, R., Stringer, A., Raber-Durlacher, J.E., & Keefe, D. (2006). Growth factors and cytokines in the prevention and treatment of oral and gastrointestinal mucositis. *Supportive Care in Cancer*, 14, 519–527. doi:10.1007/s00520-006-0052-7
- Ward, E., Smith, M., Henderson, M., Reid, U., Lewis, I., Kinsey, S., . . . Picton, S.V. (2009). The effect of high-dose enteral glutamine on the incidence and severity of mucositis in paediatric oncology patients. *European Journal of Clinical Nutrition*, 63, 134–140. doi:10.1038/sj.ejcn.1602894
- World Health Organization. (1979). *Handbook for reporting results of cancer treatment*. Geneva, Switzerland: Author.
- Worthington, H.V., Clarkson, J.E., Bryan, G., Furness, S., Glenny, A.M., Littlewood, A., . . . Khalid, T. (2011). Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database of Systematic Reviews*, 9, CD006386. doi:10.1002/14651858.CD000978.pub5
- Worthington, H.V., Clarkson, J.E., & Eden, O.B. (2004). Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database of Systematic Reviews*, 2, CD001973. doi:10.1002/14651858.CD001973.pub2
- Wu, H.G., Song, S.Y., Kim, Y.S., Oh, Y.T., Lee, C.G., Keum, K.C., . . . Lee, S.W. (2009). Therapeutic effect of recombinant human epidermal growth factor (RhEGF) on mucositis in patients undergoing radiotherapy, with or without chemotherapy, for head and neck cancer: A double-blind placebo-controlled prospective phase 2 multi-institutional clinical trial. *Cancer*, 115, 3699–3708. doi:10.1002/cncr.24414
- Yamagata, K., Arai, C., Sasaki, H., Takeuchi, Y., Onizawa, K., Yanagawa, T., . . . Bukawa, H. (2012). The effect of oral management on the severity of oral mucositis during hematopoietic SCT. *Bone Marrow Transplantation*, 47, 725–730. doi:10.1038/bmt.2011.171
- Yarom, N., Ariyawardana, A., Hovan, A., Barasch, A., Jarvis, V., Jensen, S.B., . . . Lalla, R.V. (2013). Systematic review of natural agents for the management of oral mucositis in cancer patients. *Supportive Care in Cancer*, 21, 3209–3221. doi:10.1007/s00520-013-1869-5
- Yen, S.H., Wang, L.W., Lin, Y.H., Jen, Y.M., & Chung, Y.L. (2012). Phenylbutyrate mouthwash mitigates oral mucositis during radiotherapy or chemoradiotherapy in patients with head-and-neck cancer. *International Journal of Radiation Oncology, Biology, Physics*, 82, 1463–1470. doi:10.1016/j.ijrobp.2011.04.029
- Yoneda, S., Imai, S., Hanada, N., Yamazaki, T., Senpuku, H., Ota, Y., . . . Uematsu, H. (2007). Effects of oral care on development of oral mucositis and microorganisms in patients with esophageal cancer. *Japanese Journal of Infectious Diseases*, 60, 23–28.
- You, W.C., Hsieh, C.C., & Huang, J.T. (2009). Effect of extracts from indigowood root (*Isatis indigotica* Fort.) on immune responses in radiation-induced mucositis. *Journal of Alternative and Complementary Medicine*, 15, 771–778. doi:10.1089/acm.2008.0322
- Zanin, T., Zanin, F., Carvalhosa, A.A., de Souza Castro, P.H., Pacheco, M.T., Zanin, I.C., & Brugnera, A. (2010). Use of 660-nm diode laser in the prevention and treatment of human oral mucositis induced by radiotherapy and chemotherapy. *Photomedicine and Laser Surgery*, 28, 233–237. doi:10.1089/pho.2008.2242