

Review article

Up-to-date Modalities in the Prevention of Oral Mucositis: A Literature Review

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SUMMARY

Introduction/Aim. Oral mucositis is an acute, inflammatory, and ulcerative condition of the oral mucosa caused by chemotherapy and/or radiotherapy. Considering the frequency of oral mucositis, its impact on the physical and mental health of patients, as well as the depletion of the economic capacities of an individual and society, the importance of prevention and management of oral mucositis is clearly highlighted. The aim of our study was to determine the modern preventive modalities for oral mucositis.

Literature review. A search of studies indexed in the literature from 2002 to 2022 was conducted using the PubMed database. The search was conducted with the keywords: stomatitis, mucositis, oral mucositis, chemotherapy, radiotherapy, prevention, and oral cancer. There are numerous preventive modalities for oral mucositis, including: patient education, professional oral health care, home hygiene, rinsing solutions, anti-inflammatory agents such as benzydamine, photobiomodulation, cryotherapy, miconazole, liquid mucoadhesive hydrogel, high potency polymerized cross-linked sucralfate, morphine mouthwash solution, growth factors and cytokines, honey, vitamin C, vitamin E, vitamin B2, zinc, and glutamine.

Conclusion. The following preventive modalities for oral mucositis stand out as the most significant in the literature: benzydamine, laser therapy according to the specifications available in the literature, cryotherapy, 0.2% morphine mouthwash solution, and orally administered glutamine. The variability in the results indicates the complex nature of this clinical entity and the need for additional research, which will support the existing results and enrich the literature with new preventive modalities.

Keywords: stomatitis, oral mucositis, chemotherapy, radiotherapy, prevention, oral cancer

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INTRODUCTION

With the rise of chemotherapy as a therapeutic modality in the 1940s, the number of adverse changes of the oral mucosa, generally referred to as stomatitis, increased significantly. Due to the lack of effective therapeutic methods, as well as preventive guidelines for stomatitis, the quality of life and the prognosis of these patients have continuously worsened (1). In the past, the term "stomatitis", in addition to being used for the changes that occur because of chemotherapy and/or radiotherapy, was also used for many other diseases affecting the oral mucosa. The term "mucositis" i.e., "oral mucositis" began to be used in the 1980s as a more precise term describing lesions resulting from cytotoxic cancer therapy (2). The complex pathogenetic mechanisms of the previously called stomatitis were discovered in 2007, and thus the new term "oral mucositis" was officially adopted, which described the lesions that occur because of the cytotoxic effects of chemo- and/or radiotherapy. In the same year, ICD-9 code 528.0 was assigned to lesions associated with cytotoxic cancer therapy. The ICD-10 code for oral mucositis is K12.3 (3).

Oral mucositis is an acute, inflammatory, and ulcerative condition of the oral mucosa whose incidence during chemotherapy is 40%, and in combination with radiotherapy, the incidence rate reaches a value close to 100% (4, 5). Depending on the intensity of the changes of oral mucositis, there may be a significant decrease in the quality of life of these patients due to disturbance of nutrition and sleep, communication problems, and immense pain (6). In certain cases, patients may lose consciousness because of pain and dehydration, which further necessitates stopping cancer treatment (7).

Considering the frequency of oral mucositis, its impact on the physical and mental health of patients, as well as the depletion of the economic capacities of an individual and society, the importance of prevention and management of oral mucositis is clearly highlighted (8). Since the literature indicates different preventive modalities for this clinical entity (9-18), the aim of our study was to determine the modern preventive modalities for oral mucositis.

LITERATURE REVIEW

A search of studies indexed in the literature from 2002 to 2022 was conducted using the PubMed database. The search was conducted with the keywords: stomatitis, mucositis, oral mucositis, chemotherapy, radiotherapy, prevention, and oral cancer. The data were grouped according to a frequently used division of preventive modalities for oral mucositis (19-22): 1) Basic oral hygiene; 2) Anti-inflammatory therapy; 3) Photobiomodulation; 4) Cryotherapy; 5) Antimicrobial agents, coating agents, anesthetics, and analgesics; 6) Growth factors and cytokines, and 7) Natural and miscellaneous agents. We used the additional keywords (23) for each of the separate categories: basic oral care, chlorhexidine, patient education, anti-inflammatory agents, laser therapy, low-level laser therapy (LLLT), photobiomodulation, cryotherapy, analgesics, antimicrobials, mucosal coating agents, growth factors, cytokines, natural products, honey, aloe vera, vitamin E, vitamin C, vitamin B, zinc, and glutamine. We included English-language sources that, with appropriate clinical, histological, or molecular data, evaluate the effect of the appropriate preventive agent for oral mucositis.

After searching the literature, a total of 90 sources were used for this study, including: original papers, literature reviews, systematic reviews, clinical studies, randomized controlled studies, and books.

According to the available data, the division of the different preventive modalities we used was initially introduced by the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO), which have a great contribution for the prevention and management of oral mucositis and which, in the period from 2004 to 2021, are constantly researching and renewing clinical guidelines for the prevention and treatment of chemotherapy-induced oral mucositis (19-23).

Basic oral care

When it comes to basic oral care, it is inevitable to mention patient education, professional oral

health care, as well as home hygiene and the use of different solutions for rinsing the oral cavity (24). Several studies evaluating the effect of patient education as a preventive measure for oral mucositis were available in the recent literature (25-28). The studies implement training sessions for self-assessment and maintenance of oral health with professional staff. Three studies (25, 27, 28) found that patient education significantly reduced the frequency and intensity of oral mucositis in patients with head and neck cancer and patients with hematologic-associated cancer, while a comparative study by Schmidt et al. (26) found no benefit from patient education. We believe that patient education is undoubtedly useful and may result in patient benefit despite the diversity of data from the literature.

The impact of professional oral health care in relation to oral mucositis is usually evaluated by evaluating the intensity of oral mucositis and the intensity of pain. In two studies (29, 30), a reduction in the intensity of oral mucositis was registered, while one study (31) registered a reduction in pain as a result of oral mucositis during regular implementation of professional oral health care. Dental evaluation and treatment as indicated prior to cancer therapy are desirable to reduce the risk of local and systemic infections from odontogenic sources.

Considering chlorhexidine as a rinsing solution, the available data was consistent (22, 32, 33) and indicates that chlorhexidine does not have a preventive effect on the occurrence of oral mucositis. However, this does not preclude other indications for chlorhexidine in cancer patients, such as prevention or treatment of oral infections. If chlorhexidine is indicated because of a concomitant oral infection and oral mucositis, it is acceptable to use it because of the oral infection.

Anti-inflammatory agents

When it comes to anti-inflammatory therapy and prevention of oral mucositis, the use of benzydamine solution for rinsing the oral cavity is most often mentioned in the literature. The results of numerous studies investigating the effect of benzydamine on the severity of oral mucositis are summarized in the studies of Ariyawardana et al. (34) and Nicolatou-Gallitis et al. (35) and indicate a significant reduction in the intensity of oral mucositis and pain in patients receiving chemo- and/or radiotherapy. Benzydamine exhibits anti-inflammatory properties

by inhibiting the production of pro-inflammatory cytokines such as TNF α and IL-1 β (36) which play a key role in the pathogenetic mechanisms of oral mucositis (34, 37).

Photobiomodulation

Recent data from the literature support the use of photobiomodulation for the prevention of oral mucositis, especially in bone marrow transplantation, in head and neck radiotherapy (without chemotherapy) and in head and neck radiotherapy in combination with chemotherapy (38). To achieve an optimal therapeutic effect, it is important to precisely follow the recommendations and specific settings of the laser published in the literature, which depend on the reason for therapy, as well as the type of therapy (radiotherapy or a combination of radio- and chemotherapy) (22). Bensadoun and Nair (39) recommend the use of red or infrared LLLT with diode output between 10-100 mW, dose of 2-3 J/cm²/cm² for prophylaxis and 4 J/cm² (maximum limit) for therapeutic effect, application on single spot rather than scanning motion.

Cryotherapy

Conventional methods for applying cryotherapy in the oral cavity are the use of cold water or ice, but there are other, newer methods, and commercial devices that are used in daily practice (40). Vasoconstriction caused by low temperatures reduces the transport of cytotoxic drugs to oral tissues and thus prevents secondary complications (41). Additionally, low temperatures reduce metabolic activity in the basal layer, making the epithelium less sensitive to cytotoxic agents (42).

The effects of cryotherapy have been investigated in bone marrow transplant patients (43-48), in patients with 5-FU bolus chemotherapy for solid tumors (49, 50), in patients treated with short-term infusion chemotherapy and short-half-life agents (41), and in patients treated with head and neck radiotherapy (51).

The latest guidelines recommend the use of cryotherapy in two cases: in patients undergoing autologous bone marrow transplantation treated with high doses of melphalan; in patients receiving 5-FU bolus therapy, 30 minutes during the therapy itself (22).

Antimicrobials, coating agents, anesthetics, and analgetics

Candidiasis is a common oral infection in patients with cancer and it can secondarily infect the lesions of oral mucositis, worsening the symptoms and making it difficult for them to epithelize. Therefore, it is theorized that antifungal drugs can prevent oral mucositis (52).

Rao et al. (53) in their study of 181 patients registered a reduced incidence of oral mucositis and oral candidiasis with twice weekly prophylactic administration of fluconazole during chemoradiotherapy in patients with head and neck cancer.

Miconazole is a synthetic imidazole antifungal agent that is often used to treat candidomycotic infections. However, oral medications for topical use, due to dynamics in the oral medium, need to be applied frequently, which makes it difficult for patients to cooperate and adhere to the therapeutic regimen. Therefore, Orvain et al. (54) in their study investigated the new formulation of miconazole, administered as a mucoadhesive buccal tablet, but the research was not aimed at monitoring oral mucositis, but at indirect indicators (hospitalization time, morphine use) of oral mucositis.

The oral mucosa of cancer patients is more susceptible to physiological trauma. For this purpose, coating agents have been created that form a barrier that reduces the irritation of the oral mucosa (52). Several studies of viscous liquid mucoadhesive hydrogel (MAH) are found in the literature (55-57), however, the results of these studies are not sufficient to establish official guidelines for the use of this preparation for the prevention of oral mucositis. Complete prevention and rapid elimination of oral mucositis were registered in McCullough's research (58), which opens new directions for studying the coating agent used in the study—high-potency polymerized cross-linked sucralfate (HPPCLS).

From the category of analgesics, the local use of 0.2% morphine mouthwash solution is recommended for the regulation of pain caused by oral mucositis in patients with head and neck cancer treated with chemoradiotherapy (22, 59, 60).

Growth factors and cytokines

Growth factors and cytokines can stimulate the regeneration of oral mucosa cells, preventing oral mucositis and reducing its negative effects (61). The

effects of different growth factors and cytokines have been studied in the literature, such as: granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) (62-64), epidermal growth factor (EGF) (65, 66), erythropoietin (EPO) (67), as well as the most frequently mentioned family of growth factors, which give the most favorable results keratinocyte growth factors (KGF) in the form of palifermin (68-72).

The most recent guidelines recommend the use of intravenous KGF-1 for the prevention of oral mucositis in patients with hematologic malignancies who have undergone bone marrow transplantation (22, 73). Current data do not recommend the topical use of GM-CSF for the prevention of oral mucositis in patients with hematological cancer who have undergone bone marrow transplantation (22, 74).

Natural and miscellaneous agents

Honey has often been investigated in medicine, due to its: antioxidant, anti-inflammatory, antibacterial, antiviral, antifungal, antitumor, antimutagenic, and regenerative properties (75-79).

Charalambous et al. (76) evaluated and determined the potential effect of a solution of thyme and honey to improve quality of life and improve symptoms in patients with head and neck cancer. According to Khanjani et al. (80), the use of an aqueous solution of honey (in the ratio of honey: water, 1:20) is effective for the prevention and reduction of the intensity of oral mucositis in patients with acute myeloid leukemia. Sener et al. (81) treated patients with oral mucositis with a mixture of honey and vitamin E and found that this solution better controlled oral mucositis than chlorhexidine. According to the latest guidelines (22), honey is recommended for the prevention of oral mucositis in patients with head and neck cancer treated with radiotherapy or chemoradiotherapy, but honey also has a cariogenic effect, so its application must be moderate (82).

The most common form of vitamin E— α -tocopherol has cytoprotective and anti-inflammatory characteristics (83). The efficacy of vitamin E for the prevention and regulation of oral mucositis has been investigated in different tumors/carcinomas, where it has been administered in different forms: solution for gargling and swallowing in hematological patients treated with chemotherapy (84), tablet form, and as an oil in hematological patients and patients

treated with chemotherapy (85), topical use in solid tumors treated with chemotherapy (86, 87) and in the form of a solution for gargling and swallowing in patients with head and neck cancer treated with radiotherapy (88).

Ferreira et al. (89) evaluated the prophylactic efficacy of vitamin C and vitamin B2 on methotrexate-induced gastrointestinal mucositis in an animal model. The authors (89) registered a benefit from the use of vitamin C but not from the use of vitamin B2. Rasheed et al. (90) examined the concentration of vitamin C in bone marrow transplant patients and registered a more advanced form of mucositis in patients with a lower concentration of vitamin C in the body. Kletzel et al. (91) prescribed vitamin C (2 g per day) in bone marrow transplant patients and detected an improvement in the clinical manifestation of oral mucositis and an improvement in quality of life through a pain-free diet.

In the literature, when it comes to the prevention of oral mucositis, zinc is often mentioned as an important electrolyte for the homeostasis of the body, which is involved in the processes of wound healing and the immune response of the individual (86). Chaitanya et al. (92) found in their research that zinc treatment resulted in a milder clinical presentation of oral mucositis, and vitamin C treatment resulted in less pain in the subjects. In combination, zinc and vitamin C resulted in milder clinical manifestation, less pain and better taste perception. Other studies also confirm the efficacy of zinc in the prevention of oral mucositis (93-95), however, there are also studies that indicate the absence of efficacy of zinc in the prevention of oral mucositis (96, 97). Due to the diversity of results, there are still no official guidelines for the use of zinc in the prevention of oral mucositis.

Due to the protective effect of saliva, different methods of stimulation of salivary secretion and their effect on the prevention of oral mucositis were investigated in the literature, such as: stimulation with chewing gum (98, 99), electrical stimulation (100), and intravenous application of N-acetyl cysteine (101). There is not enough evidence about the

preventive effect of the mentioned methods (98-101) in the prevention of oral mucositis.

Glutamine is an amino acid that is present in large quantities in blood plasma and plays a significant role in cell survival under conditions of metabolic stress (102). Studies in the literature evaluating the preventive effect of glutamine on oral mucositis examined it in two different forms: parenterally and per os (103-108). Considering the studies in which there is an absence of evidence of benefit from parenteral administration of glutamine, as well as one study (103) in which a higher mortality rate was recorded in cancer patients who were given parenteral glutamine, there is no support that the parenteral form of this preparation should be used for the prevention of oral mucositis. Several studies show a positive effect of orally (per os) administered glutamine in patients treated with chemo- and chemoradiotherapy (109-112), which is the supported way of using glutamine for the prevention of oral mucositis (22).

CONCLUSION

Through this research and critical evaluation of the available literature related to oral mucositis, we can note that there is considerable variation in the preventive power of different agents. Undoubtedly, patient education and regular consultations with the dentist are important for the prevention of oral mucositis, but we can single out the following agents and preventive modalities as equally important: benzydamine, laser therapy according to the specifications available in the literature, cryotherapy, 0.2% morphine mouthwash solution, and orally administered glutamine.

The variability in the results indicates the complex nature of this clinical entity and the need for additional research, which will not only support the results of previous research but also enrich the literature with new possibilities for the prevention of this complication caused by chemo- and/or radiotherapy.

References

1. Pulito C, Cristaudo A, Porta C, et al. Oral mucositis: the hidden side of cancer therapy. *J Exp Clin Cancer Res* 2020; 39(1): 210.
<https://doi.org/10.1186/s13046-020-01715-7>
2. Naidu MU, Ramana GV, Rani PU, et al. Chemotherapy-induced and/or radiation therapy-induced oral mucositis--complicating the treatment of cancer. *Neoplasia* 2004; 6(5): 423-31.
<https://doi.org/10.1593/neo.04169>
3. Shankar A, Roy S, Bhandari M, et al. Current Trends in Management of Oral Mucositis in Cancer Treatment. *Asian Pac J Cancer Prev* 2017; 18(8): 2019-26. doi: 10.22034/APJCP.2017.18.8.2019
4. Panahi Y, Ala S, Saeedi M, et al. Allopurinol mouth rinse for prophylaxis of fluorouracil-induced mucositis. *Eur J Cancer Care* 2010; 19(3): 308-12.
<https://doi.org/10.1111/j.1365-2354.2008.01042.x>
5. Rubenstein EB, Peterson DE, Schubert M, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer* 2004; 100: 2026-46.
<https://doi.org/10.1002/cncr.20163>
6. Javadzadeh BA, Pakfetrat A, Tonkaboni A, et al. Preventing and therapeutic effect of propolis in radiotherapy-induced mucositis of head and neck cancers: a triple-blind, randomized, placebo-controlled trial. *Iran J Cancer Prev* 2015; 8(5): e4019.
<https://doi.org/10.17795/ijcp-4019>
7. Hurria A, Browner IS, Cohen HJ, et al. Wildes T: Senior adult oncology. *J Natl Compr Canc Netw* 2012; 10(2): 162-209.
<https://doi.org/10.6004/jnccn.2012.0019>
8. Van der Beek MT, Laheij AM, Raber-Durlacher JE, et al. Viral loads and antiviral resistance of herpesviruses and oral ulcerations in hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2012; 47: 1222-8.
<https://doi.org/10.1038/bmt.2012.2>
9. Berger AM, Kilroy TJ. In: *Oral complications: Principles and Practice of Oncology*. 5th ed. Philadelphia PA: Lippincott Raven; 1997.
10. Verdi CJ. Cancer therapy and oral mucositis. *Drug Saf* 1993; 9: 185-95.
<https://doi.org/10.2165/00002018-199309030-00004>
11. Sonis ST. Mucositis as a biological process-a new hypothesis for the development of chemotherapy induced stomatotoxicity. *Oral Oncol* 1998; 34: 39-43.
[https://doi.org/10.1016/S1368-8375\(97\)00053-5](https://doi.org/10.1016/S1368-8375(97)00053-5)
12. Sonis ST, Lindquist L, Van Vugt A, et al. Prevention of chemotherapy-induced ulcerative mucositis by transforming growth factor beta-3. *Cancer Res* 1994; 54: 1135-8.
13. Ruescher TJ, Sodeifi A, Scrivani SJ, et al. The impact of mucositis on alpha hemolytic streptococcal infection in patients undergoing autologous bone marrow transplantation for hematologic malignancies. *Cancer* 1998; 82(11): 2275-81.
[https://doi.org/10.1002/\(SICI\)1097-0142\(19980601\)82:11<2275::AID-CNCR25>3.0.CO;2-Q](https://doi.org/10.1002/(SICI)1097-0142(19980601)82:11<2275::AID-CNCR25>3.0.CO;2-Q)
14. Sonis S, Costa JW, Jr, Evitts SM, et al. Effect of epidermal growth factor on ulcerative mucositis in hamsters that receive common chemotherapy. *Oral Surg Oral Med Oral Pathol* 1992; 74: 749-55.
[https://doi.org/10.1016/0030-4220\(92\)90402-C](https://doi.org/10.1016/0030-4220(92)90402-C)
15. Lichtman SM. Physiological aspects of aging-implication for the treatment of cancer. *Drugs Aging* 1995; 7: 212-25.
<https://doi.org/10.2165/00002512-199507030-00006>
16. Sonis ST. In: *Oral complication of cancer therapy: Principles and Practices of Oncology*. Philadelphia, PA: Lippincott; 1993.

17. Navajesh M. Xerostomia-diagnosis and treatment. *Am J Otolaryngol* 1983; 4: 283-92.
[https://doi.org/10.1016/S0196-0709\(83\)80072-6](https://doi.org/10.1016/S0196-0709(83)80072-6)
18. Olif A, Blayer WA, Poplak DG. Methotrexate induced oral mucositis and salivary methotrexate concentration. *Cancer Chemother Pharmacol* 1979; 2: 225-6.
<https://doi.org/10.1007/BF00258300>
19. Rubenstein EB, Peterson DE, Schubert M, et al. Mucositis Study Section of the Multinational Association for Supportive Care in Cancer; International Society for Oral Oncology. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer* 2004; 100(9): 2026-46.
<https://doi.org/10.1002/cncr.20163>
20. Keefe DM, Schubert MM, Elting LS, et al. Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007; 109(5): 820-31.
<https://doi.org/10.1002/cncr.22484>
21. Lalla RV, Bowen J, Barasch A, et al. Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 2014; 120(10): 1453-61.
<https://doi.org/10.1002/cncr.29174>
22. Elad S, Cheng KKF, Lalla RV, et al. Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 2020; 126(19): 4423-31.
<https://doi.org/10.1002/cncr.33100>
23. Ranna V, Cheng KKF, Castillo DA, et al. Mucositis Study group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO). Development of the MASCC/ISOO clinical practice guidelines for mucositis: an overview of the methods. *Support Care Cancer* 2019; 27(10): 3933-48.
<https://doi.org/10.1007/s00520-019-04891-1>
24. Hong CHL, Gueiros LA, Fulton JS, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer* 2019; 27(10): 3949-67.
<https://doi.org/10.1007/s00520-019-04848-4>
25. Leppla L, de Geest S, Fierz K, et al. An oral care self-management support protocol (OrCaSS) to reduce oral mucositis in hospitalized patients with acute myeloid leukemia and allogeneic hematopoietic stem cell transplantation: a randomized controlled pilot study. *Support Care Cancer* 2016; 24(2): 773-82
<https://doi.org/10.1007/s00520-015-2843-1>
26. Schmidt H, Boese S, Bauer A, et al. Interdisciplinary care programme to improve selfmanagement for cancer patients undergoing stem cell transplantation: a prospective non-randomised intervention study. *Eur J Cancer Care* 2017; 26(4).
<https://doi.org/10.1111/ecc.12458>
27. Yavuz B, Bal Yilmaz H. Investigation of the effects of planned mouth care education on the degree of oral mucositis in pediatric oncology patients. *J Pediatr Oncol Nurs* 2015; 32(1): 47-56.
<https://doi.org/10.1177/1043454214554011>
28. Yüce UÖ, Yurtsever S. Effect of Education About Oral Mucositis Given to the Cancer Patients Having Chemotherapy on Life Quality. *J Cancer Educ* 2019; 34(1): 35-40.
<https://doi.org/10.1007/s13187-017-1262-z>
29. Saito H, Watanabe Y, Sato K, et al. Effects of professional oral health care on reducing the risk of chemotherapy-induced oral mucositis. *Support Care Cancer* 2014; 22(11): 2935-40.
<https://doi.org/10.1007/s00520-014-2282-4>

30. Kashiwazaki H, Matsushita T, Sugita J, et al. Professional oral health care reduces oral mucositis and febrile neutropenia in patients treated with allogeneic bone marrow transplantation. *Support Care Cancer* 2012; 20(2): 367-73
<https://doi.org/10.1007/s00520-011-1116-x>
31. Kubota K, Kobayashi W, Sakaki H, et al. Professional oral health care reduces oral mucositis pain in patients treated by superselective intra-arterial chemotherapy concurrent with radiotherapy for oral cancer. *Support Care Cancer* 2015; 23(11): 3323-9.
<https://doi.org/10.1007/s00520-015-2774-x>
32. Cardona A, Balouch A, Abdul M, et al. Efficacy of chlorhexidine for the prevention and treatment of oral mucositis in cancer patients: a systematic review with meta-analyses. *J Oral Pathol Med* 2017; 46(9): 680-8.
<https://doi.org/10.1111/jop.12549>
33. Hashemi A, Bahrololoumi Z, Khaksar Y, et al. Mouth-rinses for the prevention of chemotherapy induced oral mucositis in children: a systematic review. *Iran J Ped Hematol Oncol* 2015; 5(2): 106-12.
34. Ariyawardana A, Cheng KKF, Kandwal A, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO). Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer* 2019; 27(10): 3985-95.
<https://doi.org/10.1007/s00520-019-04888-w>
35. Nicolatou-Galitis O, Sarri T, Bowen J, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients. *Support Care Cancer* 2013; 21(11): 3179-89.
<https://doi.org/10.1007/s00520-013-1847-y>
36. Chang JE, Min SW, Kim CS, et al. Effect of prophylactic benzydamine hydrochloride on postoperative sore throat and hoarseness after tracheal intubation using a double-lumen endobronchial tube: a randomized controlled trial. *Can J Anaesth* 2015; 62: 1097-103.
<https://doi.org/10.1007/s12630-015-0432-x>
37. Sultani M, Stringer AM, Bowen JM, et al. Antiinflammatory cytokines: important immunoregulatory factors contributing to chemotherapy-induced gastrointestinal mucositis. *Chemother Res Prac* 2012; 2012: 490804
<https://doi.org/10.1155/2012/490804>
38. Migliorati C, Hewson I, Lalla RV, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients. *Support Care Cancer* 2013; 21(1): 333-41.
<https://doi.org/10.1007/s00520-012-1605-6>
39. Bensadoun RJ, Nair RG. Low-level laser therapy in the prevention and treatment of cancer therapy-induced mucositis: 2012 state of the art based on literature review and meta-analysis. *Curr Opin Oncol* 2012; 24(4): 363-70.
<https://doi.org/10.1097/CCO.0b013e328352eaa3>
40. Walladbegi J, Gellerstedt M, Svanberg A, et al. Innovative intraoral cooling device better tolerated and equally effective as ice cooling. *Cancer Chemother Pharmacol* 2017; 80(5): 965-972. doi: 10.1007/s00280-017-3434-2. Epub 2017 Oct 3. Erratum in: *Cancer Chemother Pharmacol* 2018;81(1):225.
<https://doi.org/10.1007/s00280-017-3434-2>
41. Correa MEP, Cheng KKF, Chiang K, et al. Systematic review of oral cryotherapy for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer* 2020; 28(5): 2449-56.
<https://doi.org/10.1007/s00520-019-05217-x>
42. Walladbegi J, Smith SA, Grayson AK, et al. Cooling of the oral mucosa to prevent adverse effects of chemotherapeutic agents: An in vitro study. *J Oral Pathol Med* 2018; 47(5): 477-83.
<https://doi.org/10.1111/jop.12696>

43. Askarifar M, Lakdizaji S, Ramzi M, et al. The effects of oral cryotherapy on chemotherapy-induced oral mucositis in patients undergoing autologous transplantation of blood stem cells: a clinical trial. *Iran Red Crescent Med J* 2016; 18: e24775.
<https://doi.org/10.5812/ircmj.24775>
44. Salvador P, Azusano C, Wang L, et al. A pilot randomized controlled trial of an oral care intervention to reduce mucositis severity in stem cell transplant patients. *J Pain Symptom Manag* 2012; 44: 64-73.
<https://doi.org/10.1016/j.jpainsymman.2011.08.012>
45. Batlle M, Morgades M, Vives S, et al. Usefulness and safety of oral cryotherapy in the prevention of oral mucositis after conditioning regimens with high-dose melphalan for autologous stem cell transplantation for lymphoma and myeloma. *Eur J Haematol* 2014; 93: 487-91.
<https://doi.org/10.1111/ejh.12386>
46. Chen J, Seabrook J, Fulford A, et al. Icing oral mucositis: oral cryotherapy in multiple myeloma patients undergoing autologous hematopoietic stem cell transplant. *J Oncol Pharm Pract* 2017; 23: 116-20.
<https://doi.org/10.1177/1078155215620920>
47. Vokurka S, Chvojková I, Svoboda T, et al. The impact of oral cryotherapy and oral and gastrointestinal mucositis after autologous stem cell transplantation. *Eur J Oncol Nurs* 2014; 18: 228-9.
<https://doi.org/10.1016/j.ejon.2013.11.001>
48. Svanberg A, Ohn K, Birgegård G. Caphosol((R)) mouthwash gives no additional protection against oral mucositis compared to cryotherapy alone in stem cell transplantation. A pilot study. *Eur J Oncol Nurs* 2015; 19: 50-3.
<https://doi.org/10.1016/j.ejon.2014.07.011>
49. Katranci N, Ovayolu N, Ovayolu O, et al. Evaluation of the effect of cryotherapy in preventing oral mucositis associated with chemotherapy-a randomized controlled trial. *Eur J Oncol Nurs* 2012; 16: 339-44.
<https://doi.org/10.1016/j.ejon.2011.07.008>
50. Sorensen JB, Skovsgaard T, Bork E, et al. 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* 2008; 112: 1600-6.
<https://doi.org/10.1002/cncr.23328>
51. Kakoei SGA, Nakhaee, N. Effect of cryotherapy on oral mucositis in patients with head and neck cancers receiving radiotherapy. *Int J Radiat Res* 2013; 11: 117-20.
52. Saunders DP, Rouleau T, Cheng K, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer* 2020; 28(5): 2473-84.
<https://doi.org/10.1007/s00520-019-05181-6>
53. Rao NG, Han G, Greene JN, et al. Effect of prophylactic fluconazole on oral mucositis and candidiasis during radiation therapy for head-and-neck cancer. *Pract Radiat Oncol* 2013; 3(3): 229-33.
<https://doi.org/10.1016/j.prro.2012.05.008>
54. Orvain C, Moles-Moreau MP, François S, et al. Miconazole mucoadhesive buccal tablet in high-dose therapy with autologous stem cell transplantation (HDT/ASCT)-induced mucositis. *Support Care Cancer* 2015; 23(2): 359-64.
<https://doi.org/10.1007/s00520-014-2365-2>
55. Allison RR, Ambrad AA, Arshoun Y, et al. Multi-institutional, randomized, double-blind, placebocontrolled trial to assess the efficacy of a mucoadhesive hydrogel (MuGard) in mitigating oral mucositis symptoms in patients being treated with chemoradiation therapy for cancers of the head and neck. *Cancer* 2014; 120(9): 1433-40.
<https://doi.org/10.1002/cncr.28553>
56. Lindsay G, Rushton R, Harris T. The clinical effectiveness of Gelclair in the management of oral mucositis. *Austal Nurs J* 2009; 16: 30-3.

57. Vokurka S, Skardova J, Hruskova R, et al. 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. *Med Sci Monit* 2011; 17(10): 572-6.
<https://doi.org/10.12659/MSM.881983>
58. McCullough R. Evidence-Based Statistics on Complete Prevention and Rapid Sustained Elimination of Chemoradiation Mucositis by High-Potency Polymerized Cross-Linked Sucralfate. *J Oncol Navig Surviv* 2018; 9(2).
59. Vayne-Bossert P, Escher M, de Vautibault CG, et al. Effect of topical morphine (mouthwash) on oral pain due to chemotherapy- and/or radiotherapy-induced mucositis: a randomized double-blinded study. *J Palliat Med* 2010; 13(2): 125-8.
<https://doi.org/10.1089/jpm.2009.0195>
60. Sarvzadeh M, Hemati S, Meidani M, et al. Morphine mouthwash for the management of oral mucositis in patients with head and neck cancer. *Adv Biomed Res* 2015; 4:44.
<https://doi.org/10.4103/2277-9175.151254>
61. Riley P, Glenny AM, Worthington HV, et al. Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors. *Cochrane Database Syst Rev* 2017; 11(11).
<https://doi.org/10.1002/14651858.CD011990.pub2>
62. Pietri E, Andreis D, Fabbri F, et al. A phase II study of a dose-density regimen with fluorouracil, epirubicin, and cyclophosphamide on days 1 and 4 every 14 days with filgrastim support followed by weekly paclitaxel in women with primary breast cancer. *Oncologist* 2015; 20(3): 239-40.
<https://doi.org/10.1634/theoncologist.2014-0326>
63. Ryu JK, Swann S, LeVeque F, et al. 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. *Int J Radiat Oncol Biol Phys* 2007; 67(3): 643-50.
<https://doi.org/10.1016/j.ijrobp.2006.09.043>
64. Straka C, Sandherr M, Salwender H, et al. Testing G-CSF responsiveness predicts the individual susceptibility to infection and consecutive treatment in recipients of high-dose chemotherapy. *Blood* 2011; 117(7): 2121-8.
<https://doi.org/10.1182/blood-2010-06-290080>
65. Kim KI, Kim JW, Lee HJ, et al. Recombinant human epidermal growth factor on oral mucositis induced by intensive chemotherapy with stem cell transplantation. *Am J Hematol* 2013 ;88(2) :107-12.
<https://doi.org/10.1002/ajh.23359>
66. Wu HG, Song SY, Kim YS, et al. 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* 2009; 115(16): 3699-708.
<https://doi.org/10.1002/cncr.24414>
67. Hosseini H, Hadjibabae M, Gholami K, et al. The efficacy of erythropoietin mouthwash in prevention of oral mucositis in patients undergoing autologous hematopoietic SCT: a double-blind, randomized, placebo-controlled trial. *Hematol Oncol* 2017; 35(1): 106-12.
<https://doi.org/10.1002/hon.2250>
68. Lucchese A, Matarese G, Ghislanzoni LH, et al. Efficacy and effects of palifermin for the treatment of oral mucositis in patients affected by acute lymphoblastic leukemia. *Leuk Lymphoma* 2016; 57(4): 820-7.
<https://doi.org/10.3109/10428194.2015.1081192>
69. Lucchese A, Matarese G, Manuelli M, et al. Reliability and efficacy of palifermin in prevention and management of oral mucositis in patients with acute lymphoblastic leukemia: a randomized, double-blind controlled clinical trial. *Minerva Stomatol* 2016; 65(1): 43-50.
70. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* 2004; 351(25): 2590-8.

<https://doi.org/10.1056/NEJMoa040125>

71. Stiff PJ, Emmanouilides C, Bensinger WI, et al. Palifermin reduces patient-reported mouth and throat soreness and improves patient functioning in the hematopoietic stem-cell transplantation setting. *J Clin Oncol* 2006; 24(33): 5186-93.
<https://doi.org/10.1200/JCO.2005.02.8340>
72. Schmidt E, Thoenissen NH, Rudat A, et al. Use of palifermin for the prevention of high-dose methotrexate-induced oral mucositis. *Ann Oncol* 2008; 19(9): 1644-9.
<https://doi.org/10.1093/annonc/mdn179>
73. European Medicines Agency (EMA). Kevivance; 2019.
<https://www.ema.europa.eu/en/medicines/human/EPAR/kevivance>
74. Logan RM, Al-Azri AR, Bossi P et al. Systematic review of growth factors and cytokines for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer* 2020; 28: 2485-98.
<https://doi.org/10.1007/s00520-019-05170-9>
75. Lima ICGDS, de Fátima Souto Maior L, Gueiros LAM, et al. Clinical applicability of natural products for prevention and treatment of oral mucositis: a systematic review and meta-analysis. *Clin Oral Investig* 2021; 25(6): 4115-24.
<https://doi.org/10.1007/s00784-020-03743-1>
76. Charalambous M, Raftopoulos V, Paikousis L, et al. The effect of the use of thyme honey in minimizing radiation-induced oral mucositis in head and neck cancer patients: A randomized controlled trial. *Eur J Oncol Nurs* 2018; 34: 89-97.
<https://doi.org/10.1016/j.ejon.2018.04.003>
77. Ramsay EI, Rao S, Madathil L, et al. Honey in oral health and care: A mini review. *J Oral Biosci* 2019; 61: 32-6.
<https://doi.org/10.1016/j.job.2018.12.003>
78. Munstedt K, Momm F, Hubner J. Honey in the management of side effects of radiotherapy- or radio/chemotherapy-induced oral mucositis. A systematic review. *Complement Ther Clin Pract* 2019; 34: 145-52.
79. Yang C, Gong G, Jin E, et al. Topical application of honey in the management of chemo/radiotherapy-induced oral mucositis: A systematic review and network meta-analysis. *Int J Nurs Stud* 2019; 89, 80-7.
<https://doi.org/10.1016/j.ijnurstu.2018.08.007>
80. Khanjani Pour-Fard-Pachekenari A, Rahmani A, Ghahramanian A, et al. The effect of an oral care protocol and honey mouthwash on mucositis in acute myeloid leukemia patients undergoing chemotherapy: A single-blind clinical trial. *Clin Oral Investig* 2019; 23: 1811-21.
<https://doi.org/10.1007/s00784-018-2621-9>
81. Konuk Sener D, Aydin M, Cangur S, et al. The Effect of Oral Care with Chlorhexidine, Vitamin E and Honey on Mucositis in Pediatric Intensive Care Patients: A Randomized Controlled Trial. *J Pediatr Nurs* 2019; 45: 95-101.
<https://doi.org/10.1016/j.pedn.2019.02.001>
82. Yarom N, Hovan A, Bossi P, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (MASCC/ISOO). Systematic review of natural and miscellaneous agents, for the management of oral mucositis in cancer patients and clinical practice guidelines - part 2: honey, herbal compounds, saliva stimulants, probiotics, and miscellaneous agents. *Support Care Cancer* 2020; 28(5): 2457-72.
<https://doi.org/10.1007/s00520-019-05256-4>
83. Galli F, Azzi A, Birringer M, et al. Vitamin E: emerging aspects and new directions. *Free Radic Biol Med* 2017; 102: 16-36.
<https://doi.org/10.1016/j.freeradbiomed.2016.09.017>
84. Khurana H, Pandey RK, Saksena AK, et al. An evaluation of vitamin E and pycnogenol in children suffering from oral mucositis during cancer chemotherapy. *Oral Dis* 2013; 19: 456-64.
<https://doi.org/10.1111/odi.12024>
85. El-Housseiny AA, Saleh SM, El-Masry AA, et al. The effectiveness of vitamin "E" in the treatment of oral mucositis in children receiving chemotherapy. *J Clin Pediatr Dent* 2007; 31: 167-70.

<https://doi.org/10.17796/jcpd.31.3.r8371x45m42l10j7>

86. Yarom N, Hovan A, Bossi P, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (MASCC/ISOO). Systematic review of natural and miscellaneous agents for the management of oral mucositis in cancer patients and clinical practice guidelines-part 1: vitamins, minerals, and nutritional supplements. *Support Care Cancer* 2019; 27(10):3997-4010.
<https://doi.org/10.1007/s00520-019-04887-x>
87. Sung L, Tomlinson GA, Greenberg ML, et al. Serial controlled N-of-1 trials of topical vitamin E as prophylaxis for chemotherapy-induced oral mucositis in paediatric patients. *Eur J Cancer* 2007; 43(8): 1269-75.
<https://doi.org/10.1016/j.ejca.2007.02.001>
88. Ferreira PR, Fleck JF, Diehl A, et al. Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucositis: a double-blind randomized trial. *Head Neck* 2004; 26(4): 313-21.
<https://doi.org/10.1002/hed.10382>
89. da Silva Ferreira AR, Wardill HR, Havinga R, et al. Prophylactic Treatment with Vitamins C and B2 for Methotrexate-Induced Gastrointestinal Mucositis *Biomolecules* 2020; 11(1): 34.
<https://doi.org/10.3390/biom11010034>
90. Rasheed M, Roberts CH, Gupta G et al. Low Plasma Vitamin C Levels in Patients Undergoing Stem Cell Transplantation. *Biol Blood Marrow Transplant* 2017; 23: 286-7.
<https://doi.org/10.1016/j.bbmt.2016.12.446>
91. Kletzel M, Powers K, Hayes M. Scurvy: A new problem for patients with chronic GVHD involving mucous membranes; an easy problem to resolve. *Pediatr Transplant* 2014; 18: 524-6.
<https://doi.org/10.1111/petr.12285>
92. Chaitanya NCS, Muthukrishnan A, Kondapaneni, et al. Comparative study on the efficacy of high-dose oral ascorbic acid with/without zinc in reducing the severity of oral mucositis during cancer chemoradiation. *Oral Surg, Oral Med, Oral Pathol Oral Radiol* 2020; 129(1): 191-2.
<https://doi.org/10.1016/j.oooo.2019.07.041>
93. Ertekin MV, Koc M, Karslioglu I, et al. Zinc sulfate in the prevention of radiation-induced oropharyngeal mucositis: a prospective, placebo-controlled, randomized study. *Int J Radiat Oncol Biol Phys* 2004; 58(1): 167-74.
[https://doi.org/10.1016/S0360-3016\(03\)01562-1](https://doi.org/10.1016/S0360-3016(03)01562-1)
94. Lin LC, Que J, Lin LK, et al. Zinc supplementation to improve mucositis and dermatitis in patients after radiotherapy for head-and-neck cancers: a double-blind, randomized study. *Int J Radiat Oncol Biol Phys* 2006; 65: 745-50.
<https://doi.org/10.1016/j.ijrobp.2006.01.015>
95. Watanabe T, Ishihara M, Matsuura K, et al. Polaprezinc prevents oral mucositis associated with radiochemotherapy in patients with head and neck cancer. *Int J Cancer* 2010; 127: 1984-90.
<https://doi.org/10.1002/ijc.25200>
96. Gorgu SZ, Ilknur AF, Sercan O, et al. The effect of zinc sulphate in the prevention of radiation induced oral mucositis in patients with head and neck cancer. *Int J Radiat Res* 2013; 11: 111-6.
97. Sangthawan D, Phunggrassami T, Sinkitjarurnchai W. 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. *J Med Assoc* 2013; 96: 69-76.
98. Eghbali A, Taherkhanchi B, Bagheri B, et al. Effect of chewing gum on oral mucositis in children undergoing chemotherapy: a randomized controlled study. *Iran J Ped Hematol Oncol* 2016; 6: 9-14.
99. Gandemer V, Le Deley MC, Dollfus C, et al. Multicenter randomized trial of chewing gum for preventing oral mucositis in children receiving chemotherapy. *J Pediatr Hematol Oncol* 2007; 29: 86-94.
<https://doi.org/10.1097/MPH.0b013e318030a3e4>
100. Pimenta Amaral TM, Campos CC, Moreira dos Santos TP et al. Effect of salivary stimulation therapies on salivary flow and chemotherapy-induced mucositis: a preliminary study. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; 113: 628-37.

<https://doi.org/10.1016/j.oooo.2011.10.012>

101. Moslehi A, Taghizadeh-Ghehi M, Gholami K, et al. N-acetyl cysteine for prevention of oral mucositis in hematopoietic SCT: a double-blind, randomized, placebo-controlled trial. *Bone Marrow Transplant* 2014; 49: 818-23.
<https://doi.org/10.1038/bmt.2014.34>
102. Cluntun AA, Lukey MJ, Cerione RA, et al. Glutamine metabolism in cancer: understanding the heterogeneity. *Trends Cancer* 2017; 3: 169-80.
<https://doi.org/10.1016/j.trecan.2017.01.005>
103. Pytlik R, Benes P, Patorkova M, et al. Standardized parenteral alanylglutamine dipeptide supplementation is not beneficial in autologous transplant patients: a randomized, double-blind, placebo-controlled study. *Bone Marrow Transplant* 2002; 30: 953-61
<https://doi.org/10.1038/sj.bmt.1703759>
104. Uderzo C, Rebora P, Marrocco E, et al. Glutamine-enriched nutrition does not reduce mucosal morbidity or complications after stem-cell transplantation for childhood malignancies: a prospective randomized study. *Transplantation* 2011; 91: 1321-5.
<https://doi.org/10.1097/TP.0b013e31821ab959>
105. Piccirillo N, De Matteis S, Laurenti L, et al. Glutamine-enriched parenteral nutrition after autologous peripheral blood stem cell transplantation: effects on immune reconstitution and mucositis. *Haematologica* 2003; 88: 192-200.
106. Blijlevens NM, Donnelly JP, Naber AH, et al. A randomised, double-blinded, placebo-controlled, pilot study of parenteral glutamine for allogeneic stem cell transplant patients. *Support Care Cancer* 2005; 13: 790-6.

<https://doi.org/10.1007/s00520-005-0790-y>
107. Chattopadhyay S, Saha A, Azam M, et al. Role of oral glutamine in alleviation and prevention of radiation induced oral mucositis: a prospective randomized study. *South Asian J Cancer* 2014; 3: 8-12.
<https://doi.org/10.4103/2278-330X.126501>
108. Tsujimoto T, Yamamoto Y, Wasa M, et al. L-glutamine decreases the severity of mucositis induced by chemoradiotherapy in patients with locally advanced head and neck cancer: a double-blind, randomized, placebo-controlled trial. *Oncol Rep* 2015; 33: 33-9.
<https://doi.org/10.3892/or.2014.3564>
109. Pattanayak L, Panda N, Dash MK, et al. Management of chemoradiation-induced mucositis in head and neck cancers with oral glutamine. *J Glob Oncol* 2016; 2: 200-6.
<https://doi.org/10.1200/JGO.2015.000786>
110. Pachon Ibanez J, Pereira Cunill JL, Osorio Gomez GF, et al. Prevention of oral mucositis secondary to antineoplastic treatments in head and neck cancer by supplementation with oral glutamine. *Nutr Hosp* 2018; 35: 428-33.
<https://doi.org/10.20960/nh.1467>
111. Nihei S, Sato J, Komatsu H, et al. The efficacy of sodium azulene sulfonate L-glutamine for managing chemotherapy-induced oral mucositis in cancer patients: a prospective comparative study. *J Pharm Health Care Sci* 2018; 4: 20.
<https://doi.org/10.1186/s40780-018-0114-2>
112. Okada T, Nakajima Y, Nishikage T, et al. A prospective study of nutritional supplementation for preventing oral mucositis in cancer patients receiving chemotherapy. *Asia Pac J Clin Nutr* 2017; 26: 42-8.

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Savremeni modaliteti u prevenciji oralnog mukozitisa: pregled literature

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SAŽETAK

Uvod/Cilj. Oralni mukozitis predstavlja akutno, inflamatorno i ulcerozno stanje oralne sluzokože, koje je uzrokovano hemioterapijom i/ili radioterapijom. S obzirom na učestalost oralnih mukozitisa, njihov uticaj na fizičko i mentalno zdravlje pacijenata, kao i na crpljenje ekonomskih kapaciteta pojedinaca i društva, jasno je naglašen značaj prevencije i lečenja mukozitisa. Cilj našeg istraživanja bio je da se utvrde savremeni modaliteti u prevenciji oralnih mukozitisa.

Pregled literature. Pretraživanje indeksiranih studija od 2002. do 2022. godine sprovedeno je korišćenjem baze podataka *PubMed*. Pretraga je vršena prema sledećim ključnim rečima: stomatitis, mukozitis, oralni mukozitis, hemioterapija, radioterapija, prevencija i oralni karcinom. Postoje brojni preventivni modaliteti za oralni mukozitis, koji uključuju: edukaciju pacijenata, profesionalnu oralnu zdravstvenu zaštitu, kućnu higijenu, rastvore za ispiranje usta, antiinflamatorna sredstva poput benzidiamina, fotobiomodulaciju, krioterapiju, mikonazol, tečni mukoadhezivni hidrogel, polimerizovani visokopotentni umreženi sukralfat, rastvor morfijuma za ispiranje usta, faktore rasta i citokine, med, vitamin C, vitamin E, vitamin B2, cink i glutamin.

Zaključak. U literaturi se kao najznačajniji izdvajaju sledeći modaliteti prevencije oralnih mukozitisa: benzidiamin, terapija laserom prema uputstvima dostupnim u literaturi, krioterapija, 0,2% rastvor tečnosti za ispiranje usta na bazi morfijuma i oralno primenjeni glutamin. Varijabilnost u rezultatima ukazuje na kompleksnu prirodu ovog kliničkog entiteta i potrebu za dodatnim istraživanjima koja će potkrepiti postojeće rezultate i obogatiti literaturu novim preventivnim pristupima.

Ključne reči: stomatitis, oralni mukozitis, hemioterapija, radioterapija, prevencija, rak usne duplje