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Review Article

Nutritional management of oral mucositis in pediatric cancer patients: a narrative review

Sripriya Venkiteswaran[1]*, Purvi Kadakia[2], Sangeeta Mudaliar[3], Purnota Dutta Bahl[1], Anju Morarka[1]

[1]Cuddles Foundation, Mumbai, Maharashtra, India
[2]Department of Pediatric Hematology and Oncology, Lokmanya Tilak Municipal General Hospital, Sion, Mumbai, Maharashtra, India
[3]Department of Hematology-Oncology, B.J. Wadia Hospital, Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Sripriya Venkiteswaran,
E-mail: sripriya@cuddlesfoundation.com

ABSTRACT

Oral mucositis is a frequent and debilitating chemotherapy complication that significantly impairs oral intake and worsens nutritional status, particularly in children undergoing cancer treatment who are already nutritionally vulnerable. While numerous studies in the literature focus on the therapeutic management and prevention of mucositis, nutritional management remains an overlooked area, especially in pediatric oncology. This review aims to address this gap by examining current evidence on nutritional strategies for the management of oral mucositis in pediatric oncology, including dietary modifications tailored to disease severity and the potential role of functional foods and nutrient-based supplements. A structured literature search was conducted for studies published between January 2000 and October 2025 using suitable search terminologies and phrases. Eligible studies included randomized and non-randomized clinical trials, reviews, and primary research published in English. A two-stage screening process identified 41 studies eligible for inclusion in the final analysis. The analysis indicated that glutamine demonstrated consistent benefits in reducing the incidence and severity of oral mucositis in children receiving chemotherapy, while honey was associated with shorter duration and reduced severity of mucositis episodes. Evidence for other interventions, including vitamins, zinc, olive oil, aloe vera, and probiotics, was more heterogeneous and limited. Given the lack of clear guidance on nutritional management across mucositis severity, this review also proposes a practical severity-based dietary modification framework to support clinical care. Collectively, the findings suggest that integrating functional foods and targeted nutritional strategies may help alleviate symptoms, support oral intake, and improve supportive care in pediatric oncology patients.

Keywords: Oral mucositis, Pediatric oncology, Nutritional support, Cancer-related complications, Supportive care

INTRODUCTION

Oral mucositis is one of the most common but painful side-effects of cancer treatment. Children with hematological cancers undergoing intensive treatments, such as those with acute myeloid leukemia (AML), relapsed acute lymphoblastic leukemia (ALL), advanced lymphoma, or those undergoing hematopoietic stem cell transplantation (HSCT), are most susceptible to developing mucositis.[1] Incidence of oral mucositis is influenced by the type of cancer and treatment regimen. Attina et al (2021) have reported that the presence of neutropenia, higher number of chemotherapy cycles, and co-existence of lymphomas and sarcomas are factors increasing the risk of occurrence of oral mucositis.[2] It has been estimated that 52-100% of children undergoing high

intensity chemotherapy may be affected by oral mucositis.[2] Gandhi et al (2017) reported an incidence rate of 58.1% in children undergoing chemotherapy in a single-center study in India, identifying it as the most common oral complication.[3] Children diagnosed with hematologic malignancies tend to experience mucositis more often than those with solid tumors. In fact, this specific group of patients is at a higher risk of developing severe mucositis compared to individuals with other types of cancers.[4] Research indicates that nearly 99% of patients who undergo bone marrow transplantation with myeloablative therapies will present with mucositis.[5] Compared to adults, the incidence of mucositis appears to be higher among pediatric patients most likely due to the faster rate of cell division observed in this younger population.[4]

Characterized by inflammation of the oral mucosa and often resulting in pain, bleeding ulcers and difficulty eating, this condition can range from mild to severe. Oral mucositis if not adequately managed or prevented can adversely affect daily functioning, well-being, quality of life and can increase economic burden. It can cause significant pain and difficulty in feeding, increasing the risk of undernourishment.[2] Oral mucositis also represents a common cause of dose reduction and treatment delays.[4] It has also been reported that the development of oral mucositis can increase mortality by nearly 40% in severe cases.[6] Oral mucositis can also lead to an increased risk of infection and can often delay further chemotherapy treatment.[7] Mucositis can create an entry point for bacteria present in the oral cavity, potentially causing bacteremia with oral flora such as viridans group streptococci.[8]

Oral mucositis typically develops within 3 to 10 days after the start of chemotherapy and may last for up to 3 weeks. Symptoms often peak between days 7 and 14 and gradually subside unless exacerbated by an infection. Studies have indicated that confirmation of neutropenia is a significant predictor of mucositis and improvement may be linked to neutrophil recovery.[2-4]

A number of non-pharmacological (oral hygiene protocols, cryotherapy, photo biomodulation) and pharmacological agents (palifermin, tobramycin, polymyxin E, and amphotericin) have been proposed or been used in practice for the prevention and management of oral mucositis in children.[4-9]

Although prevention of oral mucositis should be a goal for all health care providers, not all mucositis occurrences are preventable. Therefore, once mucositis develops, treatment should focus on supportive care including adequate nutrition. The primary goals of management of oral mucositis include relieving pain, preventing infections and providing nutritional care including maintaining hydration and ensuring adequate caloric intake through enteral or parenteral nutrition.[4] While many reviews and studies in the literature, along with practice guidelines from organizations like Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO) and Pediatric Oncology Group of Ontario (POGO), emphasize the therapeutic management and prevention of mucositis, the aspect of nutritional management in children with cancer has not received the required attention.[10,11] Therefore, this review seeks to provide a comprehensive view on nutritional strategies for the management of oral mucositis, including dietary adjustments tailored to the severity of the condition. This review also seeks to highlight emerging research on functional foods and nutrients that may be of use in the management of oral mucositis.

METHODS

Literature research

The literature reviewed was published between January 2000 and October 2025 and was identified through a structured search strategy. Searches were conducted in PubMed, ScienceDirect, and JSTOR, as well as through reviews of articles in journals such as Pediatric Blood and Cancer and open-access publishers like MDPI. Key search terms included: pediatric, oncology, mucositis, oral mucositis, nutrition, nutritional, intervention, interventions, glutamine, honey, olive oil, vitamins, functional foods, clinical trial and chemotherapy. Additional relevant articles were identified from personal files and the reference lists of retrieved paper. Randomized and non-randomized clinical trials, review papers, and primary research and textbook publications in English were included. Data from conference abstracts, case reports and articles outside the scope of the research question were excluded from the analysis.

Screening was conducted in two stages. First, titles and abstracts were reviewed to exclude articles not meeting eligibility criteria. Following this, full-text review of the remaining studies was carried out to confirm inclusion. For all included studies, data extraction focused on study design, patient population, nutrition intervention details, and reported outcomes.

The exhaustive literature search across the numerous databases identified 132 studies, of which 41 were included in the final analysis after the two-stage screening process. The included studies comprised of randomized and non-randomized clinical trials, review articles, and primary research examining nutritional interventions for the prevention or management of oral mucositis in pediatric oncology patients. The findings are presented below.

Management of oral mucositis is a priority as it can have wide-ranging consequences including malnutrition, pain, poorer quality of life and treatment discontinuation or delays. This is particularly important in children with

cancer, as maintaining nutritional status is critical to recovery and overall health.

Duration of oral mucositis can range between 2 to 20 days, with a mean duration of 7.3 days in pediatric patients undergoing chemotherapy for malignancies.[2] The range highlights the variability in mucositis duration among patients with different tumour types and treatment regimens. It has also been reported that the mean recovery time from severe oral mucositis is approximately 30.6 days, indicating that while initial symptoms may resolve within a week or two, complete recovery can take longer.[12] These long durations and severity of oral mucositis and its subsequent impact on food intake can lead to significant nutritional losses, particularly in children with cancer, where maintaining adequate nutrition is critical for recovery and overall health.[2]

MANAGEMENT OF ORAL MUCOSITIS THROUGH DIETARY MODIFICATIONS

The epithelial cell lining of the entire digestive tract is particularly susceptible to the toxic effects of radiotherapy and chemotherapy due to their high turnover rates. Chemotherapy agents interfere with DNA synthesis affecting the rapidly dividing cells whereas radiation causes direct damage in the irradiated areas. The resulting mucosal injury from either type of treatments can trigger a cascade of inflammatory responses, resulting in symptoms like erythema, ulceration, and pain. Cell death and the delayed ability of the oral mucosa to heal leads to the development of oral mucositis.[13]

The painful ulcerations of mucositis cause pain, discomfort, dysphagia, a decline in the overall condition and can compromise the entire digestive tract. This can lead to higher risk of odynophagia, malnutrition, dehydration and also results in changes in mood and sleep.[12] Although pain medications, cryotherapy, maintenance of oral hygiene and antibiotics form the cornerstone of the management and treatment of oral mucositis, nutrition plays a critical role in supporting healing, maintaining strength, and preventing further complications. Tailored dietary modifications can help reduce discomfort, ensure adequate caloric and protein intake, and minimize the risk of weight loss and malnutrition.

The malnutrition that occurs as a consequence of oral mucositis can exacerbate treatment complications and delay healing processes, making nutritional intervention essential. Early and proactive nutritional support can help mitigate these risks and improve treatment outcomes in patients with oral mucositis.[14] Strategies for nutritional management of oral mucositis depend primarily on the severity of the ulceration. As mucositis becomes more severe, nutritional intake becomes increasingly compromised, necessitating tailored dietary adjustments and specialized nutritional interventions. Energy- and protein dense oral liquids and semi solid foods that are comfortable to consume are often the first choices offered to children with mucositis.

However, when oral intake becomes unsustainable due to increased severity of mucositis, enteral and parenteral nutrition needs to be provided. Enteral tube feeds are very often the feeding of choice over parenteral nutrition due to its ability to maintain gastrointestinal integrity. Parenteral nutrition is very often reserved as the last choice of feeding due to reports that indicate higher risk of infection, increased cost, and large variations in electrolyte balance that require closer monitoring.[15] Parenteral nutrition is typically reserved as severity of mucositis increases and oral intake is just not possible or when insertion of enteral tubes is considered unsafe.[14] Goals to manage oral mucositis include steps to relieve pain and prevent infection, maintain hydration, provide appropriate caloric intake through enteral or parenteral nutrition support to support healing and prevent undernourishment.[4]

The severity of mucositis is assessed using standardized scales that help assess and grade the severity of mucositis. Children's International Mucositis Evaluation Scale (ChIMES) is a tool specifically designed for children with cancer and those undergoing stem cell transplant. The tool uses parent proxy reports for children under 12 and self-reports for those 12-18 years.[16]

However, the most commonly used ones are the WHO Oral Toxicity Scale and the Common Terminology Criteria for Adverse Events (CTCAE) grading system, which evaluate symptoms like pain, ulceration, and the ability to eat and drink.[17] Common Terminology Criteria for Adverse Events (CTCAE): This tool was developed by the National Cancer Institute (NCI) and is graded on a scale from 1 to 5. It consists of two components: a functional/symptom-based evaluation and a clinical assessment.[13] The following table outlines the CTCAE grading system, detailing the severity levels and corresponding criteria used for clinical and symptom-based assessments. These tools help assess the severity of mucositis in pediatric oncology patients and it also provides the guidance to make the necessary nutritional modifications to the diet at each stage of severity. As mucositis worsens, dietary adjustments become crucial to ensure adequate nutrition while minimizing pain, discomfort and further irritation. While dietary modifications play a crucial role in managing mucositis, there are currently no well-established, standardized guidelines in the literature to guide nutritional interventions as mucositis progresses. The lack of consensus leaves a gap in clinical practice, making it essential to develop practical approaches based on available evidence and expert experience. In this context, we present a structured framework based on practical experience for dietary modifications tailored to the severity of mucositis, aiming to support better nutritional management in pediatric oncology.

Table 1: CTCAE tool for oral mucositis grading.[13]

Functional/symptoms-based exam
Grade 1 = asymptomatic or mild symptoms, and intervention is not indicated as well as the patient maintains a normal diet.
Grade 2 = moderate pain or ulcer that does not interfere with oral intake, and the patient requires a modified diet.
Grade 3 = severe pain which interferes with oral intake.
Grade 4 = life-threatening consequences that require urgent intervention.
Grade 5 = death.
Clinical exam
Grade 1 = mucosal erythema.
Grade 2 = patchy ulceration or pseudo membranes.
Grade 3 = minor trauma resulting in bleeding, confluent ulcers, or pseudo membranes.
Grade 4 = tissue necrosis, spontaneous bleeding, life-threatening events.
Grade 5 = death.

World Health Organization (WHO) Scale: The World Health Organization (WHO) scale is used to grade the severity of oral mucositis. The WHO scoring criteria include subjective and functional outcomes (pain and ability to eat) and objective signs of mucositis (ulceration and erythema).[18]

Table 2: WHO chart for oral mucositis grading.[18]

Grade 0 = no oral mucositis
Grade 1 = erythema and soreness
Grade 2 = erythema, ulcers, patient can swallow food
Grade 3 = ulcers with extensive erythema, cannot swallow food
Grade 4 = mucositis to the extent that alimentation is not possible

Table 3: Framework for dietary modifications based on severity of oral mucositis.

WHO grade	Capacity for oral intake	Dietary modification	Rationale
0	Able to eat	Maintain a balanced diet. Focus on nutrient-dense foods to support overall health during cancer treatment.	Ensure adequate intake of protein, vitamins, and minerals to support immune function and tissue repair.
1	Able to eat	Provide soft, moist and non-irritating foods. Avoid spicy, acidic, or coarse/hard foods. Frequent small meals to ensure adequate intake.	Minimize irritation to the oral mucosa due to soreness in the mouth. Soft and moist foods are easier to chew and swallow.
2	Able to eat solids and can swallow food	Soft, moist semi-solid foods. Add sauces/gravies. Avoid very hot or very cold foods. Liquid nutritional supplements should be considered if intake is poor.	Maintain caloric and nutrient intake while minimizing discomfort. Liquid supplements can help meet nutritional needs when solid food intake is reduced.
3	Unable to tolerate solid foods and cannot swallow	Liquid or pureed diet. High-calorie and protein-rich nutritional supplements. Avoid liquids that are sour or tart and may cause irritation to the mucosa. Enteral tube feeding may be required.	Ensure adequate caloric and nutrient intake when swallowing is difficult. Supplements help meet nutritional needs.
4	Alimentation not possible	Enteral tube feeding or parenteral nutrition may be indicated.	Bypass the oral cavity to provide essential nutrients and ensure nutritional status.

MANAGEMENT OF ORAL MUCOSITIS THROUGH NUTRIENTS AND FUNCTIONAL FOODS

While dietary modifications help prevent undernourishment and manage nutritional status during mucositis, a growing body of emerging research highlights the potential role of specific nutrients and functional foods in promoting healing and reducing severity. The following section explores evidence-based interventions, drawing from recent studies on key nutrients and bioactive compounds that may play a supportive and therapeutic role in managing mucositis in children.

Table 4: Summary of studies investigating prevention or treatment of oral mucositis with nutrients in pediatric oncology.

Nutrients	Study details	Author(s)	Conclusion
Glutamine	n=48 Randomized controlled study Duration of intervention: 14 days. Objective: to evaluate the efficacy of orally administered glutamine in preventing oral mucositis and reducing hospitalization costs in pediatric patients undergoing chemotherapy for ALL.	Widjaja (2020)[19]	Oral glutamine supplementation oral glutamine (400 mg/kg body weight per day) demonstrated a significant advantage over placebo in preventing oral mucositis. Additionally, hospitalization costs were lower in the glutamine-supplemented group compared to the control group.
	n=96 Retrospective study Intravenous glutamine (0.4 g/kg/day) was started within 48 h after the initiation of high dose methotrexate (HDMTX) for 3 consecutive days.	Chang (2017)[20]	Lower in the patients who received glutamine along with HDMTX compared to the control group (3.8% vs. 17.6%; p=0.004). No patients suffered from severe oral mucositis in the glutamine group.
	n=64 courses of HDMTX Cross-over trial Glutamine mouthwash was recommended twice daily using the swish-and-swallow method, beginning one day prior to the HDMTX course and continued for up to seven days or until mucositis resolved.	Sankaran (2025)[21]	Between the glutamine group and the SOHP group (71.8% vs. 81.2%; p=0.08). However, the glutamine group showed a significantly lower rate of severe mucositis (3.1% vs. 44%; RR (95% CI): 0.07 (0.01–0.35); p<0.001), a shorter median duration of mucositis (2 days (range 0–3) vs. 5 days (range 3–5); p<0.001), and lower median pain scores (4.5 (IQR 0–6) vs. 8 (IQR 5.25–8); p<0.001).
Vitamin D	n=99 Observational study Measured vitamin D levels in 99 children with ALL prior to the initiation of four cycles of chemotherapy and in 81 of these children following the discontinuation of chemotherapy	Oosterom (2018)[22]	In children with acute lymphoblastic leukemia (ALL) undergoing chemotherapy, a reduction in 25(OH)D3 levels was associated with the development of severe oral mucositis.
Vitamin E	n=80 Randomized control trial. Patients were randomly assigned to receive either topical or systemic vitamin E at a dose of 100 mg twice a day. Both groups were followed for 5 days	Elhousseiy (2007)[23]	In the group that applied vitamin E topically, 24 cases (80%), healed completely, 4 cases (13.3%) improved, and only 2 cases (6.7%) did not improve. While, in the systemic group, 31Cases (93.3%) did not improve, 2 cases (6.1%) improved, and none healed completely. The study concluded that applying 100 mg of vitamin E topically twice a day is an effective approach for managing chemotherapy-induced oral mucositis.
	n=37 Prospective study. Vitamin E in combination with ursodeoxycholic acid, folinic acid and parenteral nutrition. Vitamin E was given once daily at a dose of 8 IU/kg, 15 IU per 0.3 ml) for patients weighing less than 25 kg, and	Thornley (2004)[24]	It was observed that in the study group that there was (1) a reduced prevalence and severity of mucositis (p = 0.008 and 0.004, respectively); (2) less severe hepatic toxicity (p=0.007); and (3) a shorter time to engraftment (p= 0.02).

Continued.

Nutrients	Study details	Author(s)	Conclusion
	400 IU for those 25 kg or more. Treatment began 3 to 5 days before the start of conditioning and continued until either day 27 post-transplant or discharge from the HSCT unit, depending on which came first. Patients received this combo for a median of 33 days.		
Vitamin A	n=30 This study aimed to evaluate the potential protective effects of vitamin A supplementation on gastrointestinal mucosal integrity in pediatric recipients HSCT.	Pattanakitakul (2020)[25]	Pre-transplant vitamin A supplementation in pediatric patients undergoing HSCT did not demonstrate any clinical benefit in preserving gastrointestinal mucosal integrity.
Zinc	n=90 Randomized, double-blind, placebo-controlled trial. The objective of the study was to evaluate the efficacy and safety of oral zinc (1 mg/kg/dose) in preventing oral mucositis in children (3-18 years) with cancer receiving intensified chemotherapy. Duration of intervention was 14 days.	Shah (2023)[26]	There were no significant differences between the two groups in the severity (p=0.79), the mean time of onset (p=0.09), the mean duration of oral mucositis (p =0.18), and the need for hospitalizations (p=1.0). No significant adverse events were observed with administering oral zinc.
	n=49 Quasi-experimental study. The objective of this study was to determine the effect of oral zinc gluconate (50 mg daily) +conventional hospital treatment in oral mucositis in children with acute leukemia (8-16 years) in the early stages of oncological treatment compared to children receiving only conventional treatment. The duration of intervention was 2 months.	Gutierrez-Vargas (2020)[27]	Patients in the experimental group had, on average, 2 less days with oral mucositis than the control group (p= 0.001). The pain score was higher in the control group (p=0.0009), as was the mean score on the WHO scale (p=0.0012)

Table 5: Summary of studies investigating management of oral mucositis in pediatric oncology with functional foods.

Functional foods	Study details	Authors	Conclusion
Aloe vera and olive oil	n=36 Randomized controlled three-arms parallel-group double blind study. To assess the efficiency of aloe vera and olive oil in managing chemotherapy-induced oral mucositis. Duration of intervention: 10 days	Alkhouli (2021)[28]	Aloe vera and olive oil were shown to be effective in the management of oral mucositis
Andiroba oil	n=60 Randomized double blind trial. The	Soares	The andiroba group demonstrated a statistically significant decrease in oral mucositis severity

Continued.

Functional foods	Study details	Authors	Conclusion
	study compared the therapeutic effects of andiroba oil to low power laser treatment.	(2021)[29]	on days four, five, and six, as well as lower pain scores on days two, three, and four, when compared with the laser group following the onset of mucositis
Coconut oil	n= 60 (ages 7-26) Randomized, open-label, phase 2 clinical trial evaluating the effectiveness of virgin coconut oil mouth rinse in preventing oral mucositis in pediatric and young adult patients undergoing myeloablative conditioning for HSCT.	Clinicaltrials.gov identifier: NCT05441813. (2025)[30]	Results awaited
Honey	n=40 Randomized controlled study. This study investigates the therapeutic effects of honey in pediatric leukemia patients undergoing chemotherapy and/or radiotherapy, with a focus on grade III and IV oral mucositis, reduction of bacterial and fungal infections, and duration of oral mucositis episodes. Duration of intervention 1 year.	Al Jaouni (2017)[31]	The findings of this study demonstrated a statistically significant reduction in the frequency of oral mucositis episodes, bacterial and fungal infections, and hospital stay duration in pediatric cancer patients undergoing chemotherapy and/or radiotherapy who received honey as an adjunct to standard treatment.
	n=83 Quasi-experimental study comparing routine mouth care with or without the addition of daily wildflower honey (1g/kg).	Kobya Balut (2016)[32]	The experimental group (honey) had significantly less severe oral mucositis and a shorter recovery period compared to the control group.
	n= 100 children receiving chemotherapy who developed oral mucositis. Observational blinded study evaluating children receiving routine analgesic and antiseptic gel and the experimental group additionally receiving topical honey.	Singh (2019)[33]	Mucositis severity was observed between the two groups ($p<0.01$). The experimental group had a shorter duration of mucositis management (median 4 days, IQR† 4–6) compared with the control group (median 6 days, IQR 6–8) ($p<0.01$)
Honey, hope mixture	n= 90 patients with ALL and chemotherapy-induced oral mucositis (grades 2 and 3); mean age 6.9 years. Patients were randomized to receive topical honey, a HOPE mixture (honey, olive oil–propolis extract, beeswax), or benzocaine gel as control	Abdulrhm-an (2012)[34]	Honey significantly reduced recovery time in patients with grade 2 mucositis compared with both HOPE and control groups. For grade 3 mucositis, recovery was comparable between honey and hope, though both interventions were superior to control. Overall, honey demonstrated faster healing than either HOPE or control ($p<0.5$).
Honey and tulsi (holy basil) ice cubes	n= 40 pediatric patients with ALL undergoing chemotherapy. Randomized controlled trial evaluating the effect of either plain ice chips or honey–tulsi flavored ice chips, administered 5 minutes before methotrexate and continued for 30 minutes on severity of oral mucositis.	Mishra (2017)[35]	Both interventions significantly reduced the occurrence of oral mucositis, but the reduction was greater in the flavored ice chip group ($p < 0.001$ at both day 5 and day 15). While the severity of mucositis did not differ significantly between groups, honey–tulsi ice chips appeared more effective in reducing its occurrence.

Continued.

Functional foods	Study details	Authors	Conclusion
Olive oil	n= 24 children with ALL, aged 4–6 years. Randomized controlled clinical trial evaluating the effectiveness of topical olive oil in delaying the onset or reducing the severity of chemotherapy-induced oral mucositis in children with ALL. Children were randomized to receive either topical olive oil (4 times a day for 10 days) or sodium bicarbonate 5% applied to the oral mucosa (control group).	Alkhouli (2019)[36]	Children in the olive oil group developed mucositis later and with significantly less severity (p=0.022), suggesting that olive oil may help delay onset and reduce the severity of chemotherapy-induced oral mucositis in pediatric ALL patients.
Olive oil and honey	n=42 Single blind randomized controlled trial. To evaluate the efficacy of olive oil and honey in reducing the severity of oral mucositis and associated pain in children with leukemia. Duration of intervention 2.5 years.	Badr (2023)[37]	Children who received the honey had less severe oral mucositis (p=0.00) and less pain (p=0.00), compared to the control group. Children who received the olive oil had less pain than the control group, p=0.00), although not lower than the honey group.
Probiotics	n=11 Clinical experimental study. To evaluate the impact of probiotic mouthwash containing lactobacillus species and lactobacillus casei species, used twice daily, on oral mucositis in children with hematologic cancer undergoing chemotherapy—assessed before gargling, 7 days after gargling, and 14 days after gargling.	Christian (2020)[38]	Probiotics had a significant effect in reducing the Oral Assessment Guide scores in children with leukemia during chemotherapy and could be an alternative therapy for oral mucositis.
	n=31 (10-70 y) Phase 2 study. Study evaluated the safety and efficacy of L. Brevis CD2 lozenges in preventing oral mucositis in patients undergoing HSCT. Eligible patients received four to six lozenges of L. Brevis CD2 per day. The lozenges contained not less than 2×109 (2 billion) viable cells.4 to 7 days prior to initiation of conditioning chemotherapy and was continued till resolution of mucositis or day +24 post stem cell infusion	Sharma (2017)[39]	31 patients enrolled, 7 (22.6%) patients did not develop any mucositis, 6 (19.4%) patients developed grade 1 and 12 (38.7%) patients developed grade 2. Only six (19.4%) patients developed severe oral mucositis (grades 3 and 4); the median time to onset and for resolution of mucositis were 6 days and 8 days, respectively.

† Interquartile range

DISCUSSION

Oral mucositis is one of the most painful side effects of chemotherapy that increases the risk of infection, may prolong hospital stays, and can cause interruptions to cancer treatment.[14] For children with cancer, these effects are especially concerning because they add to an already fragile nutritional status, with potential consequences for growth, immune function, and overall treatment tolerance.[40] In this review, we bring together evidence on the three key areas of supportive care in a oral mucositis: dietary modifications, nutrient-based interventions (Table 4), and functional or bioactive food approaches (Table 5), and place these findings in the context of overall cancer

treatment. Tailoring the texture of the diet to match disease severity remains the cornerstone of nutritional management for oral mucositis. As mucositis worsens, stepwise diet modifications from a regular balanced diet (WHO Grade 0) to liquid, enteral or parenteral feeds (Grade 4) help maintain nutritional status while minimizing pain.[15] Early and proactive individualized nutrition support are crucial in children, as metabolic demands are higher and nutritional reserves are limited.

Although dietary modification offers essential support, it is often not enough on its own. This has led to an increased interest in evaluating the effect of nutrient-based and natural functional food-based approaches such as glutamine, vitamins, zinc, honey and olive oil that may in addition to providing symptomatic relief may also promote mucosal repair, enhance immune function, and potentially prevent the onset of mucositis.

Among the nutrient-based strategies studied, glutamine currently has the most convincing evidence in children. Several small clinical trials in pediatric patients with ALL receiving high-dose methotrexate have shown clear benefit. In one study, Widjaja and colleagues reported that only 4.2% of children given oral glutamine developed oral mucositis, compared with 62.5% in the control group ($p<0.001$); the glutamine group also experienced shorter hospital stays.[19]

Similarly, Chang et al (2017) demonstrated that daily supplementation at 400 mg/kg reduced the overall incidence of oral mucositis (3.8% vs 17.6%) and completely prevented severe cases.[20] More recently, an Indian crossover trial confirmed these findings, showing that a "swish and swallow" glutamine mouthwash led to a marked reduction in grade 3–4 mucositis (3.1% vs 44%) and a shorter median duration (2 vs 5 days).[21] Taken together, these results suggest that glutamine may promote mucosal healing and modulate immune response, though the limited number and size of pediatric trials underscores the need for larger, well-designed randomized studies. The need for newer well-designed studies is also highlighted due to the persistent concerns that glutamine may enhance tumour growth and survival or interact with MTX to increase toxicity, as reported in older studies.[41,42]

Fat-soluble vitamins have shown mixed results. Low vitamin D levels have been observationally linked to higher oral mucositis risk. Oosterom et al (2019) found that children whose 25(OH)D dropped during ALL therapy were more likely to develop severe oral mucositis.[22] Vitamin E appears locally beneficial: one trial showed topical vitamin E (100 mg BID) completely healed mucositis in 80% of cases, whereas systemic E offered little improvement.[23] In contrast, pre-transplant vitamin A supplementation did not prevent GI mucosal injury in pediatric HSCT patients.[25] Overall, routine use of fat-soluble vitamins for the sole purpose of preventing or reducing the severity of oral mucositis in children is unsupported by strong evidence.

With respect to zinc supplementation, findings from studies have been mixed. In a recent double-blind randomized trial involving pediatric patients receiving intensive chemotherapy, zinc showed no significant effect on the onset, duration, or severity of oral mucositis compared with placebo.[26] In contrast, a quasi-experimental study suggested that zinc gluconate reduced both the duration of mucositis and associated pain scores by nearly half ($p\approx0.001$).[27] These conflicting results indicate that while zinc's biological role in tissue repair makes it a plausible candidate, the current pediatric evidence remains inconclusive. In adults, systematic reviews describe only modest benefits from zinc however, clinical guidance has shifted over time.[43] The 2013 MASCC/ISOO guidelines offered a weak recommendation for oral zinc in adult patients with oral cancers undergoing radiation or chemoradiation, but this was reversed in the 2020 update, where zinc was no longer endorsed due to the lack of high-quality Level I and II evidence.[44] This underscores how recommendations evolve as new evidence emerges, and in the case of zinc, larger, well-designed pediatric trials are still required before routine use can be justified.

Functional foods and bioactive compounds; such as honey, olive oil and probiotics have also gained increasing attention as supportive strategies for pediatric oral mucositis. Among these, honey is by far the most extensively investigated. Several pediatric trials have shown that both oral and topical honey can reduce the frequency, severity, and duration of oral mucositis. In randomized studies of children with leukaemia, honey use was associated with shorter episodes of mucositis and fewer infections. For example, Singh and colleagues (2019) reported that children receiving honey had a median oral mucositis duration of four days, compared with six days in controls ($p<0.01$).[33]

A recent meta-analysis of five pediatric trials including approximately 316 patients further reinforced these findings, showing that honey shortened healing time by about five days on average and significantly reduced the risk of developing both any-grade oral mucositis ($RR\approx0.19$) and severe grade III–IV oral mucositis ($RR\approx0.18$).[45] Combining honey with other bioactives such as beeswax has also shown benefit. In a randomized study of 90 children with ALL and grades 2–3 mucositis, both honey and HOPE was better than the control group. However, the authors report that honey led to better recovery and faster healing compared with HOPE or the control group.[34] Honey flavoured ice chips administered 5 minutes before methotrexate and continued for 30 minutes have also been shown to significantly ($p<0.001$ at both day 5 and day 15) prevent oral mucositis in children with cancer although it did not affect the severity of mucositis.[35] These results point to honey as a simple and potentially valuable supportive care option,

especially in children. Due to its familiarity and palatability, topical honey may also achieve better adherence in children with oral mucositis compared to other medical options. On a cautionary note, honey theoretically poses a risk of causing botulism infection in immunocompromised children. However, the 2020 MASCC/ISOO clinical practice guidelines do provide moderate evidence (Level of Evidence 2) for honey as a preventive agent of oral mucositis in adult head and neck patients receiving chemotherapy and or radiation.[46] The 2021 MASCC/ISOO practice guidelines that followed which involved a sub-analysis of the pediatric studies discusses the speculative role of honey in preventing oral mucositis in children while also raising concerns on its ability to cause dental caries.[47] Therefore, due to considerable heterogeneity between studies, relatively small sample sizes, lesser number of studies in the pediatric population, and variations in honey formulations and administration protocols the generalizability of these results may be limited and use of honey as a standard line of care in oral mucositis prevention needs to be closely monitored.

Other natural products that have potential include olive oil which has been shown to delay the onset of oral mucositis and reduce its severity in children with ALL with one trial demonstrating significantly later onset and milder mucositis compared to controls ($p=0.022$).[36] A combination of olive oil with honey and polyphenols has also been tested, with evidence suggesting improvements in pain relief, although honey alone appeared to provide the greatest benefit.[37]

Aloe vera gel which is known for its wound healing properties due to its property of epithelial regeneration has demonstrated similar promise. In a randomized trial of 36 pediatric patients, both aloe vera and olive oil significantly improved mucositis scores compared with placebo.[28] Andiroba oil, an extract derived from the Amazonian tree Carapa guianensis, has even been shown to outperform low-level laser therapy in Brazilian children, producing lower mucositis grades on days 4–6 and reduced pain on days 2–4.[29] Virgin coconut oil, often used as a home remedy, is under investigation but results from the trial data are still awaited.[30] Probiotics represent another emerging area of interest. A small Indonesian study (n=11) using a Lactobacillus-based mouthwash in children with leukaemia found significant improvements in mucositis scores.[38] In a study by Sharma et al (2017) patients in the age range of 10-70 years, undergoing hematopoietic stem cell transplantation benefited from Lactobacillus brevis CD2 lozenges that reduced both the incidence of severe oral mucositis (grade 3–4) and its duration.[39] Together, these findings suggest that modulating the oral microbiome could be a promising strategy, however given the general trepidation with probiotic usage in paediatrics especially in immunocompromised children, variety of probiotics available and species and strain specific effects, larger, well-controlled pediatric trials are warranted.[48]

CONCLUSION

In summary, functional foods and bioactive agents appear to provide encouraging results in children, with honey and glutamine showing the most consistent benefit. Dietary modification should not be viewed as symptomatic care alone but as a platform for integrating adjunctive therapies. Honey rinses, glutamine swish-and-swallow regimens, or oil-based mucosal coatings can be layered onto modified diets to relieve pain and support continued intake during oral mucositis. This combined, staged approach may offer the most practical and sustainable strategy for preserving nutrition while reducing the impact of oral mucositis in pediatric oncology.

While this manuscript was in preparation, a systematic review on this topic reported conclusions largely consistent with our findings, particularly regarding the potential benefits of topical, nutrition-based interventions.[49] Our review compliments this by providing a severity-based dietary management approach for oral mucositis which remains largely unaddressed. Together, these two review papers reiterate the importance of exploring the potential of low-cost topical management and prevention strategies while highlighting the need for larger, standardized, multicentre trials and implementation-focused research in children.

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