Oral Glutamine Supplementation in Head and Neck Cancer Patients Undergoing Radiation Therapy

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Abstract

Background: Oral mucositis is a very common, severe side effect of radiation therapy, for which treatment options are limited. Multiple primary research studies have been completed to examine the potential role of oral glutamine supplementation in the care of head and neck cancer patients undergoing radiation therapy. The objective of this evidence analysis review was to determine if currently published research provides support for the use of oral glutamine supplementation in head and neck cancer patients undergoing radiation therapy to achieve a decrease in incidence or severity of oral mucositis.

Methods: This project followed the Academy of Nutrition and Dietetics' Evidence Analysis Process. A comprehensive search of available primary research was executed, followed by an appraisal of each article, synthesis of the evidence, and a conclusion statement about the strength of the overall research.

Results: Ten studies met the inclusion criteria. Eight studies were found to have significantly positive results; however, only two of those studies were determined to have a positive quality rating, while the other six had neutral quality ratings. In contrast, two studies did not produce significantly positive results, one of which was positively rated and one which was rated as neutral. This necessitates the need for further, well controlled trials before a strong conclusion regarding the routine use of this supplement for the HNC population can be made.

Conclusion: Currently, there is limited evidence to support the use of oral glutamine to reduce incidence or severity of radiation-induced oral mucositis in head and neck cancer patients.

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I would like to thank my family for their support throughout my academic career, as well as my professors who have challenged me to always put forth my best work and maintain a critical mind when analyzing research.

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Chapter 1: Introduction

Each year there are about 650,000 new cases of head and neck cancer around the world, and 330,000 deaths caused by this disease (Bray et al., 2018). Head and neck cancer may be treated with surgery, chemotherapy, radiation therapy, or a combination of these (National Cancer Institute, 2017). Radiation therapy, as well as chemotherapy, can put a patient at risk for multiple different side effects, one clinically significant and common side effect being mucositis (Pachón Ibáñez et al., 2018).

Mucositis can negatively impact nutrition status by causing problems with swallowing and pain, which can ultimately lead to weight loss, dehydration, hospital stays, and higher costs of medical care (Pachón Ibáñez et al., 2018). Unfortunately, no optimal treatment for mucositis has been identified, and various treatment options usually need to be combined to be effective (Rodriguez-Caballero et al., 2012). Agents that have been investigated for a potential role in combatting cancer treatment-induced oral mucositis include oral hygiene care, topical agents (antiseptics and antimicrobial), anti-inflammatory agents, cytokines, growth factors, and non-pharmacological agents such as dietary supplements (Rodriguez-Caballero et al., 2012).

One dietary supplement that has been studied for its potential use as a relatively inexpensive treatment for oral mucositis is glutamine. This non-essential amino acid is the most common amino acid in the body and functions in multiple ways, including as a building block of proteins, in amino acid transamination, and in support of the immune system (Roth, 2008). The body may be deficient in glutamine during cancer treatment, as cells use more glutamine for immune and other functions during this type of hyper-catabolic state (Cruzat et al., 2018).

Multiple primary research studies have been completed to examine the potential role of glutamine supplementation in the care of head and neck cancer patients undergoing radiation therapy. The objective of this evidence analysis review was to determine if currently published research provides support for the use of oral glutamine supplementation in head and neck cancer patients undergoing radiation therapy to achieve a decrease in incidence or severity of oral mucositis.

Research Questions

1. Does oral glutamine supplementation decrease the incidence of oral mucositis in adult head and neck cancer patients undergoing radiation therapy?
2. Does oral glutamine supplementation decrease severity of oral mucositis in adult head and neck cancer patients undergoing radiation therapy?

Nature of the Research Project

This project followed the Academy of Nutrition and Dietetics' Evidence Analysis Process (Academy of Nutrition and Dietetics, 2016). A comprehensive search of available primary research was executed, followed by an appraisal of each article, synthesis of the evidence, and a conclusion statement about the strength of the overall research.

Assumptions

The assumptions of this project included that radiation-induced oral mucositis continues to be a serious side effect of radiation therapy without a highly successful intervention, thus necessitating the continued investigation into possible treatments. This is currently the case, as various treatments for this condition have had variable outcomes and are usually reactive and symptomatic (Sroussi et al., 2017). This researcher also assumed that the glutamine

supplementation used in the studies evaluated was of high quality and purity. This was not explicitly described in the studies. In addition, it was assumed that the researchers in each study reported their data honestly and accurately, and that the patients in each study were honest with their report of compliance to interventions and study parameters. Finally, this project assumed that the Academy of Nutrition and Dietetics' Evidence Analysis process continues to be recognized as a high-quality way to critically analyze data in the field for practice application, as it has been up to this point.

Limitations

This project was limited by the current research because identified studies did not all specify the type of radiation used, and thus may vary from study to study. Additionally, dose, frequency, and duration of radiation treatment were not consistent across all studies. The use of chemotherapy (including type and dosage) was also not consistent from study to study, which was an issue because chemotherapy could increase risk of mucositis. Suboptimal oral hygiene, lower than average nutritional status, no antibiotic use early in OM, and smoking history, may all also contribute to the development of OM (Luo. et al., 2005) and were not each adequately controlled for in the studies found. Further, it was not determined if the participants of any of the studies were deficient in glutamine at baseline. Glutamine status at baseline, and throughout cancer treatment, could affect the impact glutamine supplementation has. Finally, although the studies were conducted in five different countries (Spain, Turkey, Taiwan, India and Japan) none were conducted in the United States which may limit applicability of the results to this country's population.

Delimitations

This evidence analysis only included primary research studies that used an intervention of oral glutamine supplementation with adult patients diagnosed with head and neck cancer, who were receiving radiation therapy. Studies examining only patients with cancers other than head and neck were excluded, however studies with at least partial populations of head and neck cancer patients were included. Studies examining patients only undergoing chemotherapy and not radiation were also excluded. Finally, studies that were not available in English language were excluded, as well as any study not found in the databases searched.

Search Strategy

The databases used in this project were Ebscohost and Primo. Search terms included: "oral mucositis" and "glutamine"; "oral mucositis" and "l-glutamine"; "mucositis" and "glutamine". Any systematic reviews found during the search were also reviewed for potential primary articles to be included in this project.

Definition of Terms

Chemotherapy: type of drug used to kill cancer cells (Mayo Clinic, 2020)

Glutamine: nonessential amino acid that is important for cell proliferation and survival during metabolic stress (Yarom et al., 2019)

Head and Neck Cancer (HNC): cancers of the lip, oral cavity, salivary glands, pharynx, larynx, skull base, nasal cavity, and ear (National Cancer Institute, 2017)

Oral Mucositis (OM): inflammation of the oral cavity, which can progress from erythema to ulcerations (Sroussi et al., 2017)

Radiation Therapy (RT): used to treat cancer and involves beans of intense energy (X-rays, protons, or another type) directed at cancer cells to cause cell death (Mayo Clinic, 2020)

Significance

Oral mucositis can cause a multitude of complications for a cancer patient, including pain, dysphagia, inadequate nutritional intake, decreased quality of life, breaks in cancer treatments (Pathak, Soni, Sharma, Patni, & Gupta, 2019) and possibly even poorer treatment outcomes (Elad, Zadik & Yarom, 2017). If the research shows that glutamine is an effective treatment for oral mucositis, this non-pharmacologic agent could potentially prevent or reduce some of these issues. An additional benefit would be the relatively low cost of glutamine. One glutamine supplement found online sells for $28.75 for a container of 500 grams of l-glutamine (Medtrition, 2020). It could cost an individual between $28.75 and $86.25 (plus tax and shipping fees if applicable) to use 8 to 30 grams daily of this product for the duration of a typical radiation therapy treatment length of 6 to 7 weeks (Sroussi et al., 2017). This dosage range reflects the amount used in the articles reviewed in this project.

Chapter 2: Review of the Literature

Introduction

Cancer is the cause of one in four deaths each year in the United States (Marian, Mattox, & Williams, 2017). The seventh most prevalent type of cancer is head and neck cancer (HNC); this group of cancers is comprised of several types of cancer, of mostly gastrointestinal primary origin, including lip, oral cavity (several sub-types), salivary glands, and pharynx. Other types of HNC without a primary origin within the gastrointestinal system are cancers of the larynx, skull base, nasal cavity, and ear. About 53,000 individuals in the United States develop HNC each year, with 10,800 deaths annually related to the disease (Siegal, Miller, & Jemal, 2019).

Individuals with HNC are at risk nutritionally, largely due to the common impacts the malignant tumors and/or treatments have on chewing and swallowing abilities (Marian et al., 2017). Approximately 75-80% of individuals will experience weight loss during treatment for HNC and almost all individuals are malnourished at the time of diagnosis (Schoeff, Barett, DeLassus Gress, & Jameson, 2013).

One common side effect of HNC treatment that can make consuming adequate oral nutrition challenging is oral mucositis (OM). Mucositis affects 85-100% of HNC patients treated with RT with or without chemotherapy and is the main cause of discontinuation of treatment in this patient population (Pachon Ibanez et al., 2018). This condition involves inflammation of the oral cavity due to radiation therapy (RT) or chemotherapy. It can cause mouth sensitivity and discomfort with eating and drinking, and thus put patients at risk for malnutrition.

Unfortunately, at this time treatments used for OM are suboptimal (Sroussi et al., 2017). Thus, many agents are being investigated for their possible use. One possible treatment that has been researched is the amino acid glutamine (Yarom et al., 2019). The purpose of this chapter is to outline evidence on the impact of glutamine supplementation on OM in adult HNC patients undergoing RT.

Background

Head and Neck Cancer

HNC is responsible for about 3% of malignancies in the United States (Siegel et al., 2019). The most common types of HNC are squamous cell carcinomas (SCC), found in the mucosal cells that line the upper gastrointestinal tract including the mouth, throat, and nose (National Cancer Institute, 2017).

HNC occurs twice as frequently in men than in women and is more commonly diagnosed after the age of 50 (NCI, 2017). However, HNC is becoming more common in young, non-smokers, with human papillomavirus playing a role in the etiology for this population (Poon & Stenson, 2019). A history of tobacco and/or alcohol use is common among those diagnosed with HNC (Marian et al., 2017). One meta-analysis of 28 studies found that the odds ratios of HNC were 1.29, 2.67, and 6.63 (95% CI) for light, moderate, and heavy drinkers, respectively, when compared to non/occasional drinkers (Zhang et al., 2015). This meta-analysis also found that the odds ratios of HNC were 2.33, 4.97, and 6.77 (95% CI) for light, moderate, and heavy smokers, respectively, when compared to non/occasional smokers (Zhang et al., 2015). Use of both alcohol and tobacco results in a higher risk of HNC than if only one substance was used (Memorial Sloan Kettering Cancer Center, 2020). Betel (also known as areca) nut chewing,

which is common in India and other southeast Asian countries, also contributes to risk of HNC (Muttagi, Chaturvedi, Gaikwad, Singh, & Pawar, 2012). Some evidence also suggests a genetic factor may contribute to the likelihood that an individual will develop HNC from tobacco use (Poon & Stenson, 2019). Other recognized risk factors for HNC include: low consumption of fruits and vegetables, high consumption of salt-cured fish or meat, Plummer-Vinson syndrome, Epstein-Barr virus exposure, Asian ancestry, consumption of yerba mate (a caffeinated South American beverage), suboptimal oral hygiene, inhaled exposure to multiple particles including asbestos, wood dust, nickel alloy dust, and silica dust, gastroesophageal reflux disease, a compromised immune system, graft versus host disease, and lichen planus disease (Memorial Sloan Kettering Cancer, 2020).

Multiple studies have been completed to examine the role of diet and the development of HNC. Boeing et al. used data from seven European countries to complete a prospective study that found an inverse association between total fruit and vegetable intake and risk for HNC (Boeing et al., 2006). Freedman et al. also completed a large prospective cohort study using National Institute of Health - American Association of Retired Persons (AARP) data in the United States and found an inverse association between risk of upper aero-digestive tract cancer and total fruit and vegetable intake (Freedman et al., 2008). Researchers reported the results were consistent with prior case control trials.

Aspects of the diet may also increase the risk of HNC. Farrow et al. completed a case control study in the U.S. and found an increased risk of nasopharyngeal cancer in individuals who often ate preserved meat (Farrow et al., 1998).

Symptoms of Head and Neck Cancer and of Cancer Treatment

Depending on primary location of the tumor, symptoms of HNC may include the following: non-healing sore or mass, hoarse voice or difficulty speaking, difficulty breathing, pain, swelling, unusual bleeding, headaches, chronic sinus infections, ear pain, trouble hearing or ringing in the ears (NCI, 2017). Many of these symptoms may contribute to a patient's reduced appetite or desire to eat. Additional possible symptoms of HNC that can more directly cause a risk of inadequate nutrition include dysphagia, difficulty chewing and numbness or paralysis of the face or neck (NCI, 2017).

In addition to the multiple possible symptoms from the cancer itself, many cancer treatments can also have debilitating side effects. Radiation treatment (RT) to the head and neck can cause mucositis, thick secretions, mucosal opportunistic infections, pain, and sensory disorders (Sroussi et al., 2017). Additional long-term side effects of RT can include tissue fibrosis, impairment in salivary gland function, increased risk of mucosal infections and dental carries, pain, and sensory impairments (Sroussi et al., 2017). Chemotherapy, which can be used in combination with RT, also presents a host of possible side effects that could contribute to risk of malnutrition. Depending on type and dose of chemotherapy used, possible side effects usually include fatigue, loss of appetite, nausea, vomiting, diarrhea, and constipation, among others (Mayo Clinic, 2020).

Oral Mucositis

OM is one significant side effect of HNC RT that occurs in 80% or more of patients and can increase risk of malnutrition due to the pain this side effect causes with eating and drinking (Maria, Eliopoulos, & Muanza, 2017). OM involves inflammation of the oral cavity and can progress from presence of erythema to painful ulcerations (Sroussi et al., 2017). This condition

is caused by a loss of basal layer stem cells which affects normal replacement of superficial mucosal layer cells (Galloway & Amdur, 2020). The understanding of OM pathophysiology is limited (Maria, Eliopoulos, & Muanza, 2017). It may present within or after the first two weeks of RT and last until 2-4 weeks after the last RT session (Maria, Eliopoulos, & Muanza, 2017).

The use of concurrent chemotherapy during RT is one risk factor for OM and can also cause OM to occur earlier in treatment and last longer (Sroussi et al., 2017). Additional risk factors for severe RT-induced OM include suboptimal oral hygiene, lower than average nutritional status, no antibiotic use early in OM, smoking history (Luo. et al., 2005), and renal disease (Eilers & Million, 2007). Tumor location may also play a role in risk of OM. One study found that tumor location in the oral cavity was related to higher incidence of OM in comparison to tumors of the supraglottis, glottis, or hypopharynx (Pachon Ibanez et al., 2018).

OM can cause cancer treatments to be missed, cancelled or reduced in strength, all of which can negatively affect a patient's outcomes (Sroussi et al., 2017). Further, OM can increase the cost of health care for a patient by increasing the need for hospital stays and/or emergency department visits (Sroussi et al., 2017). It has been shown that 35% of patients with RT-induced OM have had to have their treatment doses reduced or completely stopped, and 62% of those with RT-induced OM have been found to require hospitalization (Sonis et al., 2004).

Oral Mucositis Grading

The severity of oral mucositis is quantified by a numerical grade, with the increasing grade indicating more severe presentation. There are multiple ways to measure the severity grade. Table 1 below shows two methods of grading OM that are frequently used in research,

one by the National Cancer Institute Common Terminology Criteria for Adverse Events or NCI-CTC (version 5.0), and the other by the World Health Organization (WHO) (as cited by Maria, Eliopoulos, & Muanza, 2017). The NCI-CTC version 5.0 was created from a combination of a previous version and another grading scale from the Radiation Therapy Oncology Group (RTOG) (as cited by Maria, Eliopoulos, & Muanza, 2017).

Table 1.

Various Methods for Grading Oral Mucositis (as cited by Maria, Eliopoulos & Maunza, 2017)

Mucositis Grade	World Health Organization (WHO) criteria	National Cancer Institute Common Toxicity Criteria (NCI-CTC) criteria
1	Soreness +/- erythema	Erythema of the mucosa
2	Erythema, ulcers, and patient can swallow solid food	Patchy reaction (patches <1.5 cm in diameter), non-contiguous
3	Ulcers with extensive erythema and patient cannot swallow solid food	Confluent reaction, > 1.5 cm diameter, contiguous
4	Mucositis to the extent that alimentation is not possible	Necrosis or deep ulceration +/- bleeding

Nutritional Strategies for Oral Mucositis

The more severe OM becomes, the harder it can be for an individual to orally consume adequate nutrients. Nutrition support via a feeding tube may or may not be used in these patients. Data is limited regarding when the optimal time to place a feeding tube is, and thus the decision is often made on a case-by-case basis, including assessment of clinical condition and patient-involved decision making (Jatoi & Loprinzi, 2019). It is important to note that some patients may elect to not have a feeding tube placed despite a recommendation for one, and thus they must rely solely on oral intake for nutrition.

There are diet guidelines for patients suffering from OM that aim to make oral intake more tolerable and support healing and maintenance of nutritional needs. Acidic foods such as citrus juices, sharp foods such as chips, caffeinated beverages, and alcohol should be limited or avoided (Galloway & Amdur, 2020). Hot, spicy, greasy, or fried foods, and carbonated beverages may also need to be avoided if bothersome (Oncolink, 2018). In addition to foods that should be avoided, patients are provided with foods they should consume often. These include soft high-calorie, high-protein foods such as dairy, well-cooked meats, poultry, nut butters, eggs, beans and nutritional shake supplements (Oncolink, 2018).

Treatments and Cost of Oral Mucositis

Evidence-based treatments for RT-induced OM in the HNC population are suboptimal but improving. They include excellent oral care, medications and mouthwashes to reduce pain and inflammation, dietary supplements, as well as low-level laser therapy (Sroussi et al., 2017). Despite the limited approaches available, guidelines for treatment of RT-induced OM in HNC have previously been published and were recently updated. The most recent version of the guidelines, published by the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO), was released in 2019 in a series of publications (Ariyawardana et al., 2019; Bowen et al., 2019a, 2019b; Elad, 2019; Hong et al., 2019; Ranna et al., 2019; Yarom et al., 2019; Zadik et al., 2019). Evidence was determined to be one of three levels: recommendation (level I), suggestion (level II), or no guideline possible (level III).

The 2019 MASCC/ISOO guidelines have several recommendations specific to RT-induced OM in the HNC population. They include the following:

1. Benzydamine, an anti-inflammatory mouthwash, is recommended for use in preventing OM in those receiving moderate amounts of RT (<50 Gy), level of evidence I (Ariyawardana et al., 2019).
2. Benzydamine is suggested for prevention of OM in HNC patients receiving RT and chemotherapy, level of evidence II.
3. Intra-oral photobiomodulation (PBM), which refers to therapy with various forms of nonionizing light sources, is another form of OM treatment that has been investigated and is included in the published guidelines (Zadik et al., 2019). The panel recommends its use, specifically in the form of low-level laser therapy, for prevention of OM in HNC patients undergoing RT, level of evidence II. This therapy is also recommended for HNC patients undergoing RT with chemotherapy, level of evidence I. The panel acknowledged that putting these recommendations into practice may be hindered by practical and economic issues such as cost, equipment/facility requirements, training, local regulations and device availability.
4. The guidelines suggest the use of multi-agent combination oral care protocols for prevention of RT-induced OM in HNC, level of evidence II (Hong et al., 2019). According to the guidelines, these types of protocols vary, but uniformly include regular teeth brushing during cancer treatment and routine assessment of OM, and may also include rinses such as “magic mouthwashes”. Per expert opinion, the guidelines also suggest the use of routine dental care and patient education on importance of basic oral care, despite limited evidence on these topics.

5. The guidelines suggest the use of oral glutamine to prevent OM in HNC patients undergoing RT and chemotherapy, level of evidence II (Yarom et al., 2019). No other vitamins, minerals, or nutritional supplements are included in any guidelines from the panel. A previous suggestion from the 2014 guidelines for the use of zinc for HNC patients receiving RT or chemotherapy was changed and now is assigned as level III evidence- no guideline possible.

A review focused on treating OM in HNC patients found that no single agent is helpful by itself, but individual treatments must be combined in order to produce a positive effect on OM for the HNC population (Rodriguez-Caballero et al., 2012). Since the publication of that review, additional therapies have been studied and recommended, such as the low-level laser therapy outlined above. However, the MASCC/ISOO panel acknowledged in their most recent guidelines that continued research is needed to improve treatment of OM (Bowen et al., 2019a). This highlights the need to continue studying possible agents so that an ideal treatment or combination of treatments can be identified. Further, identifying an optimal treatment regimen could reduce the cost of healthcare for HNC patients. One study found that HNC patients who developed severe radiochemotherapy-associated OM or pharyngitis needed more medical care and had higher medical costs during cancer treatment than those who did not have these side effects (Nonzee et al., 2008). Researchers found that the median cost per patient for an individual who developed OM or pharyngitis was more than $18,000 higher than for a patient without these complications.

Glutamine

As mentioned previously, the amino acid glutamine is one non-pharmacologic agent that has been investigated for possible prevention and treatment of OM in the HNC population. It has also been studied as a possible treatment for esophagitis in other cancer populations such as lung cancer, esophageal cancer, and lymphoma (Vidal-Casariego, Calleja-Fernandez, Ballesteros-Pomar & Cano-Rodriguez, 2013).

In the body, the liver and skeletal muscle contain the most glutamine, accounting for approximately 40-60% (Cruzat, Rogero, Keane, Curi & Newsholme, 2018). The liver, skeletal muscle, adipose tissue, brain, and lungs can all synthesize glutamine; in contrast, the intestinal mucosa, leukocytes, and renal tubule cells are glutamine-consuming tissues (Cruzat, Rogero, Keane, Curi & Newsholme, 2018). The gut is a major site of glutamine use, as both the small and large intestines metabolize a significant amount of glutamine either from the diet or endogenous production (Cruzat, Rogero, Keane, Curi & Newsholme, 2018). Free glutamine (i.e. from a dietary supplement) is utilized most by enterocytes rather than being transported to other cells; in contrast, glutamine that is absorbed with other amino acids (either in combination as a dipeptide or as individual various amino acids) is more often sent into the blood stream to be delivered to other tissues (Cruzat, Rogero, Keane, Curi & Newsholme, 2018).

Glutamine functions by helping to increase cell proliferation, especially for the immune system and gastrointestinal mucosa, and increases cell survival during metabolic stress (Lopez-Vaquero et al., 2017). Additionally, in hyper-catabolic states (such as some cancers), immune and other cells need and use more glutamine, however endogenous synthesis of glutamine may be reduced, potentially putting the body at risk of deficiency (Cruzat, Rogero, Keane, Curi & Newsholme, 2018).

Glutamine status can be difficult to assess and should be estimated based on a full nutritional assessment that takes into consideration intake and overall clinical status (Cruzat, Rogero, Keane, Curi & Newsholme, 2018). Plasma glutamine does not necessarily reflect total body stores of this amino acid, even in hyper-catabolic states, and should not be the sole indicator for exogenous supplementation (Cruzat, Rogero, Keane, Curi & Newsholme, 2018).

The recently published MASCC/ISOO guidelines provide a suggestion for the use of oral glutamine for the prevention of OM in HNC patients undergoing RT and chemotherapy (Yarom et al., 2019). However, the literature review completed for the glutamine supplementation guideline only included recent studies published through mid-2016, and thus the guidelines only included two randomized trials by Chattopadhyay, Saha, Azam, Mukherjee & Sur (2014) and by Tsujimoto et al. (2015). Since the development of these guidelines there have been additional trials completed on glutamine supplementation in RT patients. These additional studies warrant an updated review of all available research to determine whether the level of evidence can be strengthened or reduced.

Evidence for Glutamine Supplementation in Head and Neck Cancer

Evidence for the use of glutamine supplementation is presented first in this chapter, ordered from weakest to strongest study design, followed by evidence against the use of this supplement.

Retrospective Studies

Two retrospective studies were found that assessed the use of oral glutamine for HNC patients undergoing RT with or without chemotherapy. Both studies had positive results. A 2013 retrospective cohort study, completed in Spain, evaluated 79 individuals with tumors of

the head and neck (78 with HNC and 1 with melanoma) and 38 patients with tumors in the chest area (29 with lung cancer, 6 with esophageal cancer and 3 with lymphoma) (Vidal-Casariego, Calleja-Fernandez, Ballesteros-Pomar & Cano-Rodriguez, 2013). Researchers sought to determine if oral glutamine supplementation prevents OM or RT-induced radiation esophagitis, decreases the severity of either, helps maintain nutrition status, and/or decreases RT treatment interruptions. The intervention examined was 30 grams of glutamine, taken orally each day. The intervention cohort was further split into two groups, one who started the supplement "early" (initiated before and continuing throughout RT), and the other who started the supplement in a "delayed" fashion (started after RT initiated due to late referral to the Nutrition department).

Almost half of the HNC patients received the glutamine in a "delayed" fashion (43%), about a third received it "early" (34.2%), and the last 22.8% did not receive any glutamine (Vidal-Casariego, Calleja-Fernandez, Ballesteros-Pomar & Cano-Rodriguez, 2013). The HNC patient cohort received RT at a median dose of 65 (60-70) Gy over 33 sessions. Sixty-two percent of these patients received chemotherapy in addition to the RT (chemotherapy agents/regimens were not specified). Researchers reported that in the incidence of mucositis was lower in the glutamine groups compared to the no glutamine group (risk difference of developing OM was -9%, 95% CI). Additionally, OM was significantly less severe (p=0.039) in the group that received the early glutamine supplementation. Significantly less weight loss during RT was noted in the group that received "early" glutamine (-6.6%) compared to the "delayed" glutamine group (-11.3%) and the no intervention group (-13.4%) (p=0.009). Significantly more patients in the no treatment group required tube feeding than in the "delayed" group or in the

"early" group (23.5%, 2.9% and 0.0%, respectively; p=0.04). No association was found between glutamine supplementation and the number of RT treatment interruptions.

In the RT-induced esophagitis cohort of patients, RT treatment was completed over 22-30 sessions of 42-60 Gy (Vidal-Casariego, Calleja-Fernandez, Ballesteros-Pomar & Cano-Rodriguez, 2013). Over 97% of these patients received chemotherapy in addition to RT. 63.1% received "delayed" administration of glutamine, 23.7% received no glutamine, and only 13.2% received early glutamine. Researchers found that "early" use of glutamine was associated with decreased risk of esophagitis. Significantly fewer patients (P = 0.027) had a weight loss of more than 5% in either of the treatment groups compared to the no intervention group.

Based on their results, the researchers concluded that glutamine use was associated with significant reduction in the risk and severity of OM, weight loss, and tube feeding use (Vidal-Casariego, Calleja-Fernandez, Ballesteros-Pomar & Cano-Rodriguez, 2013). They also concluded that glutamine use was associated with significantly decreased risk of RT-induced esophagitis.

Akmansu, Iren, and Gunturkun (2018) also completed a retrospective study of HNC patients, with the aim of the research being to determine the relationships between glutamine supplementation and intensity and duration of OM, and on proinflammatory cytokines. Their study, completed in Turkey, involved twenty-eight patients with cancers of either the nasopharynx, larynx, oropharynx, or hypopharynx, all who received RT with or without chemotherapy (various agents and regimens). Eighteen of the twenty-eight patients received the intervention of powdered glutamine, 10 grams taken orally every 8 hours, mixed with water

or fruit juice, from the first to last day of RT. Serum IL-1 beta, I-6, and TNF-alpha levels were measured at baseline, during the treatment and at conclusion of the cancer treatment.

The researchers found a significantly lower incidence of severe mucositis (grade 3 or worse) in the group receiving the glutamine supplementation (p=0.008). Those in the glutamine group also had significantly longer time to onset of OM (p=0.007). Further, OM occurred at a significantly higher median RT dose in the glutamine group than in the non-glutamine group (p=0.006). All 10 individuals in the non-intervention group experienced grade 2 or worse mucositis. 9 of the 18 individuals in the intervention group experienced grade 2 or worse mucositis, but the other 9 experienced grade 1 or no mucositis. The serum pro-inflammatory levels measured showed no significant differences. The authors concluded that glutamine supplementation was well tolerated, has proven effects on OM, and should be investigated further for its possible effects on inflammation (Akmansu, Iren & Gunturkin, 2018).

Prospective Cohort Research

One prospective cohort study completed in Spain yielded results in support of oral glutamine supplementation. The study was completed by Pachon Ibanez et al. and included 262 HNC patients with stage I-IV cancers of the oral cavity, oropharynx, supraglottis, glottis, nasopharynx, hypopharynx, or paranasal sinuses (Pachon Ibanez et al., 2018). Researchers sought to evaluate the relationship between incidence of OM and oral glutamine supplementation, with secondary objectives of determining incidence of odynophagia, cancer treatment interruptions, and need for analgesia and nasogastric tubes. The intervention for this study was a dosage of 10 grams of glutamine, taken orally every 8 hours throughout RT by patients in the treatment group. The control group received nothing. Twenty-five percent of

the glutamine group and 21% of the control group received only RT. The other participants received either chemotherapy, surgery, or a monoclonal antibody drug (Cetuximab) in addition to RT, though no significant differences between groups were noted. The length of the intervention was not specified. Seventy Gy given in 2 Gy/day radiation sessions was used for all patients, and chemotherapy agent and dosing varied for those it was used for. It was not stated how it was verified that all doses of glutamine were taken.

Researchers found that those not receiving the glutamine had a relative risk (RR) of developing mucositis of 1.78 (95% CI, p=0.047) in comparison to the group receiving the supplement (Pachon Ibanez et al., 2018). The intervention group also showed a significantly decreased need for nasogastric tube feeding (p=0.02), cancer treatment discontinuation (p=0.002), and prescriptions for analgesia (p=0.03). Multivariate analysis found two variables associated with the incidence of OM: tumor location and glutamine supplementation. Malignancies of the oral cavity were associated with a significantly higher incidence of mucositis than cancers of the supraglottis, glottis, or hypopharynx. Odynophagia was present in significantly more participants in the control group versus the intervention group (77.9% versus 55.7%, p= 0.0001). The glutamine group had significantly less incidence of grade III-IV (severe) odynophagia (12.2% versus 42.7% of the control group, p <0.0001). Multivariate analysis found that tumor location, glutamine supplementation, and chemotherapy use were all associated with incidence of odynophagia. Researchers concluded that oral glutamine significantly decreased incidence of OM, as well as incidence and severity of odynophagia.

Randomized Controlled Trials on Oral Glutamine

In addition to the two retrospective studies and one prospective cohort study, five randomized controlled trials (RCTs) have been published with results that support use of oral glutamine supplementation. The first was a small, single-blind, placebo-controlled trial completed in Taiwan by E. Huang et al. that evaluated the effect of oral glutamine supplementation on OM in 17 patients with HNC of the nasopharynx, oropharynx, or oral cavity (E. Huang, 2000). Patients received the same RT treatment of 25 fractions of 1.8 Gy/fraction, five days per week, with no other cancer treatments during the study. Patients were instructed to swish and then spit out 2 grams of glutamine powder in 30 ml of normal saline, four times per day, throughout their RT treatment. It was not stated if compliance to the intervention was measured. Researchers found a significantly less severe and significantly shorter duration of objective OM in the glutamine group ($p=0.006$), as well as significantly shorter time of duration of subjective grade 3 or higher (severe) OM ($p=0.0386$). Researchers concluded that severity and duration of objective OM may be significantly reduced by oral glutamine supplementation.

Chattopadhyay et al. completed an RCT in India of 70 HNC patients with stage I-IV cancers of the oral cavity, larynx, hypopharynx, nasopharynx, or oropharynx who underwent RT with or without chemotherapy (Chattopadhyay, Saha, Azam, Mukherjee & Sur, 2014). Participants received external beam RT at 2 Gy/fraction. Researchers sought to compare the effect of oral glutamine supplementation on OM. This study utilized an intervention of 10 grams of glutamine powder suspended in 1000 mL of water which was swished and swallowed daily on cancer treatment days (five days per week) 2 hours before the start of treatment. Researchers included patients who were able to take in an average 800 of the 1000 ml of

solution. The length of cancer treatment was not specified; however, it was individualized as researchers stopped the RT when grade III or IV mucositis developed.

Researchers found that the intervention group had significantly less frequent grade III OM ($p=0.02$) and grade IV OM ($p=0.04$), significantly longer time to onset of OM ($p<0.001$) and significantly shorter duration of severe (grade III or worse) OM ($p<0.001$) (Chattopadhyay, Saha, Azam, Mukherjee & Sur, 2014). However, when analyzed by treatment, patients receiving only RT and taking glutamine did not experience a statistically significant difference in severity of OM in comparison to those not taking glutamine. In contrast, those in the intervention group who received chemotherapy and RT experienced significantly less severe (grade III or IV) OM than those in the control group receiving both chemotherapy and RT ($p = 0.03$ for grade III OM and $p = 0.02$ for grade IV OM). In their conclusion, researchers acknowledged their positive findings while cautioning the need for future studies with larger samples prior to glutamine becoming standard treatment protocol.

Pathak et al. completed an RCT in India of 56 HNC patients with stage III-IV oropharynx or larynx cancer (Pathak, Soni, Sharma, Patni & Gupta, 2019). The researchers sought to examine the role and efficacy of oral glutamine supplementation on OM and dysphagia in these patients while they underwent concurrent chemoradiation. Time to onset of OM and dysphagia, incidence of treatment interruptions (defined as more than three RT sessions missed in a row), and significant weight reduction (defined as more than 3 kilograms from the beginning of the study) were secondary objectives. All participants received 70 Gy in 35 fractions and concurrent cisplatin consisting of weekly injection doses based on body surface

area. A dose of 10 grams of glutamine once per day, taken orally (or through feeding tube if needed), throughout each participant's 7-week cancer treatment was prescribed. The glutamine was only taken on RT treatment days (five days per week). The researchers did not state how it was verified that the glutamine was ingested.

The results showed significantly less severe OM in the group who received the glutamine at the seventh week of treatment ($p< 0.001$), as well as significantly longer time to onset of these symptoms (Pathak, Soni, Sharma, Patni & Gupta, 2019). They also found that the treatment group had less severe dysphagia and a longer time to onset of dysphagia (p values < 0.05 assessed at weeks 2, 4, 6, and 7 of treatment). Finally, the treatment group had significantly less participants who experienced weight loss ($p=0.004$), significantly less treatment interruptions ($p=0.025$), need for nasogastric tube feeding ($p=0.03$), and incidence of severe toxicity (need for hospital admission, $p=0.03$). The research team acknowledged the need for larger, multicentric, double-blinded studies on oral glutamine to prove their findings.

Pattanayak et al. completed an RCT in India in 2016 with 162 HNC patients with stage II-IV cancers of the oral cavity, oropharynx, hypopharynx, larynx, or nasopharynx (Pattanayak, Panda, Dash Mohanty & Samantaray, 2016). The investigators' aim was to examine the efficacy and safety of oral glutamine supplementation on HNC patients undergoing chemoradiation over seven weeks. All participants received the exact same cancer treatment regimens, however the length of treatment varied due to tolerance of therapy. Treatment consisted of concurrent chemotherapy (weekly cisplatin with dosing based on body surface area) and a goal of 70 Gy external-beam RT given in 35 fractions using a shrinking field technique. The

intervention in this group was similar to that of Chattopadhyay et al. in that the participants were instructed to swish and swallow the glutamine suspended in water. The dose in this trial was slightly higher at 15 grams given twice per day throughout treatment, each time given in a glass of water. The authors did not state how it was verified that each dose was consumed.

Researchers found that the glutamine supplementation significantly decreases severity of and delayed time to onset of OM ($p<0.05$) (Pattanayak, Panda, Dash Mohanty & Samantaray, 2016). Additionally, they reported that adverse events such as pain, dysphagia, nausea, edema, and cough were significantly more common in the control group than in the intervention group. Researchers concluded that oral glutamine is a feasible and affordable treatment for OM.

One study with positive results was found with the optimal design of a double-blind, randomized, placebo-controlled trial. This trial was completed in Japan by Tsujimoto et al. (2015) with 40 HNC patients with stage II-IV cancers of the nasopharynx, oropharynx, hypopharynx, or larynx. The aim of the study was to evaluate if glutamine decreases the severity of OM, as well as mucositis of the pharynx and larynx, for patients undergoing a standardized treatment of 6 weeks of chemotherapy and radiation. Secondary objectives were to determine duration and time to onset of mucositis, pain, incidence and duration of opioid use, total opioid dose, need for and duration of nutritional supplementation via feeding tube or peripheral parenteral nutrition, and clinical data. Patients received 66 or 70 Gy at 2 Gy/fraction, through five fractions per week. Chemotherapy treatment consisted of cisplatin and docetzel, both dosed based on body surface area. An intervention of 10 grams of glutamine, taken orally (or through a feeding tube if needed), three times per day (at 7:00, 11:00, and 16:00)

throughout cancer treatment was given to the treatment group; the control group received 10 grams of a placebo three times per day. The researchers did not specify how it was verified that the patients received all required doses, but they indicated a compliance rate of 99.6%, as measured by a pharmacist.

The researchers found that glutamine significantly decreased the maximal mucositis grade (severity) (intervention group, 2.9+/-0.3; placebo group, 3.3+/-0.4; p=0.005) (Tsujimoto et al., 2015). No significant differences were found in time to onset of mucositis, duration of mucositis, or mean time to onset of severe mucositis. The average mucositis grade was significantly higher in the placebo group at weeks 5 and 6 (p=0.027, p=0.002, respectively). During weeks 4, 5 and 6, pain scores were significantly lower in the intervention group than in the placebo group (p=0.049, p=0.019, p=0.032, respectively). Additionally, the average length of time opioids were used was significantly longer in the placebo group than in the intervention group (p=0.029). No significant difference in average total opioid dose was found between the two groups. The average length of time that nutrition supplementation was needed was significantly longer in the placebo group compared to the intervention group (p=0.046). No significant changes in average BMI or total daily caloric intake were reported. The intervention group had an average weight change of -3.6% from baseline to week 8, in comparison to a change of -6.0% in the placebo group, though this was not significant. Researchers also noted that there was no significant difference between amino acid profiles that were assessed from the intervention or placebo groups.

Researchers concluded that glutamine can significantly decrease chemoradiotherapy-induced mucositis severity in individuals with HNC. They also noted the importance of a multidisciplinary approach to care, stating that it can contribute to improved outcomes and improved patient quality of life.

Randomized Controlled Trial on Parenteral Glutamine

One final, double-blinded, placebo-controlled RCT was completed that yielded positive results. This trial was completed in Argentina by Cerchietti et al. (2006) and examined parenteral glutamine supplementation rather than oral glutamine. Researchers designed this study to determine whether supplementation with L-alanyl-L-glutamine is safe and effective for reducing incidence of OM in patients with stage III-IV HNC of the oral cavity/sinus, nasopharynx, oropharynx, or other. All patients received two induction chemotherapy cycles of cisplatin and 5-FU, followed by concurrent outpatient chemo-radiotherapy of the same chemotherapy drugs, and 70 Gy total dose of RT. Twenty-nine patients were enrolled, fourteen receiving the intervention and fifteen receiving a placebo. For the intervention group, L-alanyl-L-glutamine 0.4 g/kg weight/day was diluted in normal saline and infused over 4 hours on chemotherapy days (which occurred about weekly throughout the study).

Researchers found significantly less incidence of severe OM ($p=0.042$) in the glutamine group, as well as significantly less pain ($p=0.008$), need for opioids ($p=0.025$) and need for feeding tubes ($p=0.020$) (Cerchietti et al., 2006). The use of IV glutamine also did not produce any negative side effects during the randomized trial or in the pilot study the researchers completed before the randomized trial to asses for tolerance. The researchers concluded that

intravenous glutamine may be effective at decreasing severity of OM in HNC patients receiving treatments with high risk of OM.

No other studies using parenteral administration of glutamine for OM in HNC were found. There have been studies completed with other cancer populations however, including one such trial with a pediatric bone marrow transplant population, which found significant statistical correlation of glutamine treatment with cancer relapse (p=0.02) and a correlation with mortality (p=0.05) (Pytlik et al., 2002). The outcome of tht study has likely decreased desire to research parenteral administration of glutamine. Tsujimoto et al. also noted that availability and cost of intravenous treatment could contribute to decreased chance of widespread use when compared to oral glutamine (Tsujimoto et al., 2015).

Evidence against Glutamine Supplementation in Head and Neck Cancer

Randomized Controlled Trials on Oral Glutamine

Two randomized, double-blinded, placebo-controlled trials were found that did not support the use of oral glutamine supplementation. C. Huang et al. studied 64 patients in Taiwan with stage I-IV HNC. Most patients (65.6%) had oral cavity cancer, but diagnoses also included nasopharynx, oropharynx, hypopharynx, and larynx cancers (C. Huang et al., 2019). The aim of the study was to examine whether oral glutamine decreased OM and neck dermatitis while patients underwent intensity-modulated RT of 60-70 Gy total, given in 2 Gy fractions, with or without chemotherapy. Although the total number of individuals who did or did not receive chemotherapy did not differ significantly between groups, the type and frequency of chemotherapy may have, as this information was not provided in the study.

Researchers reported that cisplatin or carboplatin were used, with or without the addition of 5-fluorouracil. Additionally, chemotherapy may have been given weekly or every 3 weeks depending on the patient. The intervention group took a self-administered dose of 10 grams of glutamine dissolved in cold water orally (or through a feeding tube if needed) three times per day before a meal starting 1 week before RT and ending 2 weeks after RT completion. The length of the treatment was not specified, and likely varied between patients given the RT and chemotherapy (if used) was individualized for the patient.

The researchers found a decreased mean maximum severity of mucositis in the treatment group compared with placebo; however, the difference was not significant (analysis of completers, p=0.169; PP multivariate analysis, p = 0.172) (C. Huang et al., 2019). The authors acknowledged that the higher percentage of participants with oral cavity cancer in their study (versus none in the study by Tsujimoto et al.) may have contributed to this result not being significant, since the oral mucosa tissue receives a higher amount of RT in these patients. The authors also did not find any significant difference in incidence or severity of dermatitis between the intervention and placebo group. According to the researchers, another important finding of the study was that a strong correlation was found between decrease in BMI and severity of OM when multivariate PP analysis was performed (p = 0.014), as they reported that this was the first study to show such a strong correlation. They concluded that further research is warranted on oral glutamine.

One other double-blind, placebo-controlled RCT was found that did not yield significantly positive results (Lopez-Vaquero, Guitierrez-Bayard, Rodriguez-Ruiz, Saldana-Valderas, & Infante-Cossio, 2017). This study was completed in Spain and included forty-nine

patients with HNC of the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx, who were randomized to either receive ten grams of oral glutamine dissolved in water three times daily with meals, or placebo (maltodextrin). Researchers sought to examine if the glutamine would reduce incidence or severity of OM and dermatitis when the patients underwent RT with or without chemotherapy for six weeks. Patients received 66 Gy or 70 Gy RT (depending on if a patient was post-surgical), dosed at 2 Gy/fraction. If chemotherapy was used cisplatin or cetuximab was administered, with dose based on body surface area. The researchers indicated that there were no significant differences between groups for cancer treatment regimens. A 100% compliance rate to the intervention was recorded by the main researcher, who also performed a count of bags used in the trial.

Outcomes of the study included that the researchers did not find a significant difference in incidence or severity of OM between groups, although the placebo group had higher values for both (Lopez-Vaquero, Guitierrez-Bayard, Rodriguez-Ruiz, Saldana-Valderas, & Infante-Cossio, 2017). Interestingly, they did find that the glutamine group had significantly less incidence and severity of dermatitis ($p=0.038$ and $p=0.032$, respectively). The authors of this study concluded that slight clinical effects in reducing OM were seen with the use of oral glutamine, though results were not significant. Additionally, benefit was seen in reducing incidence and severity of dermatitis, however more research is warranted on glutamine's use for both clinical symptoms.

Randomized Controlled Trial on Oral Glutamine Combined with Beta-Hydroxy-Beta-Methylbutyrate and Arginine

One phase II, non-randomized trial that did not have significantly positive results was found that utilized an oral nutrition supplement that included a combination of glutamine, beta-hydroxy-beta-methylbutyrate (HMB) and arginine (Yokota et al., 2018). One of the metabolites of leucine, HMB is often used to increase muscle strength and reduce muscle protein catabolism (Memorial Sloan Kettering Cancer Center, 2020). Arginine is an amino acid created in the body that has vasodilatory properties, and has also been used to improve wound healing, enhance immunity, and improve athletic performance (Memorial Sloan Kettering Cancer Center, 2020). Additional review of research on arginine and HMB is out of the scope of this review; however, this single trial is worth noting given its use of glutamine, despite the inability to extract the singular possible effect of glutamine on the study's outcomes.

This trial was completed in Germany and sought to determine if this combination supplement could prevent OM caused by chemoradiotherapy in HNC (Yokota et al., 2018). Patients had a diagnosis of HNC of the nasopharynx, oropharynx, hypopharynx, larynx, or tongue/oral cavity. All patients received 60-70 Gy of RT, and cisplatin chemotherapy (varying frequency of administration). Thirty-five patients were included in the study and all received the intervention of 24 mg of HMB/arginine/glutamine (1.2 grams of HMB, 7 grams of arginine, and 7 grams of glutamine) mixed in 240-300 ml of water, taken twice per day, throughout the duration of RT treatment. If unable to swallow the supplement was mixed with 120 ml of water and given through a feeding tube.

Researchers found that grade 3 OM was present in sixteen patients during the trial (45.7%), and no patients developed grade IV OM (Yokota et al., 2018). The authors concluded that no statistically significant support for this supplement on the prevention of OM could be

obtained from this study. There was no control in this study, rather they used a historical group from a previous study for comparison.

Summary and Conclusions

Glutamine supplementation has been investigated for many years for its possible use as an inexpensive, non-pharmacologic agent to combat OM in HNC patients receiving RT with or without chemotherapy. The most recent MASCC/ISOO guidelines include a suggestion to use oral glutamine to prevent RT and chemotherapy-induced OM, which was updated from the 2014 guideline report when no guideline was able to be given for this supplement. However, since the completion of this guideline update, several more trials on oral glutamine have been published and have been considered in the body of evidence evaluated in this review. Eight total studies (two retrospective studies, one prospective cohort study, and five RCTs) were reviewed that support the use of oral glutamine supplementation. However, two recent RCTs that showed no significant evidence for the use of oral glutamine were also reviewed. Additionally, one study showed positive results when parenteral glutamine was used instead of oral. And finally, one study showed no significant effect of oral glutamine, when used in combination with two other components, HMB and arginine.

In the following chapter, the methods for this evidence analysis will be reviewed. The ten studies presented in this chapter that examined the use of oral glutamine will be analyzed further in Chapter 4. A discussion of the results of this analysis will follow in Chapter 5.

Chapter 3: Methodology

This evidence analysis project was completed using the Academy of Nutrition and Dietetics' Evidence Analysis Process. This is a five-step process that is rigorous and systematic, and analyzes research on a given nutrition topic, allowing conclusions and best practice recommendations to be generated (Academy of Nutrition and Dietetics, 2016). Once the Evidence Analysis Process is completed for a given nutrition topic, the results can be found in the Evidence Analysis Library (EAL), which is accessible to all members of the Academy of Nutrition and Dietetics.

AND Evidence Analysis Process

The Academy of Nutrition and Dietetics has specified five steps for the Evidence Analysis Process (Academy of Nutrition and Dietetics, 2016):

Step 1: Formulate a research question

Step 2: Create and execute a comprehensive search strategy, and classify evidence

Step 3: Appraise each research article

Step 4: Summarize the research

Step 5: Develop a conclusion statement and assign grade of strength for available evidence

Step 1.

Step 1 involves establishing a focused research question that is relevant and answerable (Academy of Nutrition and Dietetics, 2016). Existing research on a nutrition topic should be reviewed, with a goal of finding the research gaps. When possible, the PICO format should be used for the research question (problem, intervention, comparator, and outcome). The

Nutrition Care Process steps (Assessment, Diagnosis, Intervention, Monitoring and Evaluation) should be utilized when considering each part of the research question.

Table 2

PICO Formatting of the Research Questions

PICO Component	Question 1	Question 2
(P) Population	Adult HNC Patients Undergoing RT	Adult HNC Patients Undergoing RT
(I) Intervention	Oral Glutamine Supplementation	Oral Glutamine Supplementation
(C) Comparison Intervention	No Supplementation	No Supplementation
(O) Outcome	Incidence of OM	Severity of OM

Research questions for this evidence analysis project included the following:

1. Does oral glutamine supplementation decrease the incidence of oral mucositis in adult head and neck cancer patients undergoing radiation therapy?
2. Does oral glutamine supplementation decrease the severity of oral mucositis in adult head and neck cancer patients undergoing radiation therapy?

Step 2.

Step 2 of the Evidence Analysis Process is to create a comprehensive search strategy to gather all pertinent primary research relating to the research question (Academy of Nutrition and Dietetics, 2016). Inclusion and exclusion criteria need to be defined, search terms should be determined, and multiple sources should be used to find research articles. Each article that results from a specific search term should be assessed to determine if it meets inclusion criteria and lists of included and excluded articles should be created. The list of excluded articles should denote why each article was not included. Finally, each article should be classified using the Hierarchy and Classification of Studies Table found on page 32 of the Evidence Analysis Manual.

The Search Plan and Results used for this evidence analysis are detailed in Table 2 below. The classification of each study can be found on the corresponding Evidence Analysis Worksheet in Appendix 1.

Table 3

Search Plan and Results

Questions

1. Does oral glutamine supplementation decrease incidence of oral mucositis in adult head and neck cancer patients undergoing radiation therapy?
2. Does oral glutamine supplementation decrease severity of oral mucositis in adult head and neck cancer patients undergoing radiation therapy?

Date of Literature Review for the Evidence Analysis

March 2020

Inclusion Criteria

- Oral glutamine supplementation
- Adults age 18 years or older
- Diagnosis of head and neck cancer for at least part of study population (those without head and neck cancer may have another type of cancer)
- Radiation therapy with or without chemotherapy
- Primary, peer-reviewed articles

Exclusion Criteria

- Studies on populations without head and neck cancer
- Chemotherapy without radiation therapy
- Parenteral glutamine supplementation
- Persons under 18 years of age
- Publications not available in English
- Studies on animals

Search Terms: "oral mucositis" and "glutamine"; "oral mucositis" and "l-glutamine"; "mucositis" and "glutamine"

Electronic Databases Used:

- MEDLINE, ALT HealthWatch, and Academic Search Premier via Ebscohost

- Primo

Articles to review:

- "oral mucositis" and "glutamine": 30 hits in Primo, 100 hits in Ebscohost
- "oral mucositis" and "l-glutamine": 6 hits in Primo, 52 hits in Ebscohost
- "mucositis" and "glutamine": 66 hits in Primo, 156 hits in Ebscohost
- Articles in Ebscohost were filtered by Scholarly Journals

Articles Included:

AKMANSU, M., İREN, S., & GÜNTÜRKÜN, G. (2018). The Effect of Using Oral Glutamine on the Side Effect of Mucositis in Patients with Head and Neck Cancer Who Are Receiving Chemoradiotherapy: Retrospective Evaluation with Clinical and Immunological Parameters. *Turkish Journal of Oncology / Türk Onkoloji Dergisi*, *33*(3), 115–121. https://doi.org/10.5505/tjo.2018.1803

Chattopadhyay, S., Saha, A., Azam, M., Mukherjee, A., & Sur, P. (2014). Role of oral glutamine in alleviation and prevention of radiation-induced oral mucositis: A prospective randomized study. *South Asian Journal of Cancer, 3*(1), 8–12. https://doi.org/10.4103/2278-330X.126501

Huang, C., Huang, M., Fang, P., Chen, F., Wang, Y., Chen, C., … Lee, H. (2019). Randomized double-blind, placebo-controlled trial evaluating oral glutamine on radiation-induced oral mucositis and dermatitis in head and neck cancer patients. *The American Journal of Clinical Nutrition, 109*(3), 606–614. https://doi.org/10.1093/ajcn/nqy329

Huang, E., Leung, S., Wang, C., Chen, H., Sun, L., Fang, F., … Hsiung, C. (2000). Oral glutamine to alleviate radiation-induced oral mucositis: a pilot randomized trial. *International Journal of Radiation Oncology, Biology, Physics*, *46*(3), 535–539. https://doi.org/10.1016/S0360-3016(99)00402-2

Lopez-Vaquero, D., Gutierrez-Bayard, L., Rodriguez-Ruiz, J.-A., Saldaña-Valderas, M., & Infante-Cossio, P. (2017). Double-blind randomized study of oral glutamine on the management of radio/chemotherapy-induced mucositis and dermatitis in head and neck cancer. *Molecular and Clinical Oncology, 6*(6), 931–936. https://doi.org/10.3892/mco.2017.1238

Pachón Ibáñez, J., Pereira Cunill, J., Osorio Gómez, G., Irles Rocamora, J., Serrano Aguayo, P., Quintana Ángel, B., … García Luna, P. (2018). Prevention of oral mucositis secondary to antineoplastic treatments in head and neck cancer by supplementation with oral glutamine. *Nutricion Hospitalaria, 35*(2), 428–433. https://doi.org/10.20960/nh.1467

Pathak, S., Soni, T., Sharma, L., Patni, N., & Gupta, A. (2019). A Randomized Controlled Trial to Evaluate the Role and Efficacy of Oral Glutamine in the Treatment of Chemo-radiotherapy-induced Oral Mucositis and Dysphagia in Patients with Oropharynx and Larynx Carcinoma. *Cureus*, *11*(6), e4855. https://doi.org/10.7759/cureus.4855

Pattanayak, L., Panda, N., Dash, M. K., Mohanty, S., & Samantaray, S. (2016). Management of Chemoradiation-Induced Mucositis in Head and Neck Cancers With Oral Glutamine. *Journal of Global Oncology, 2(*4), 200–206. https://doi.org/10.1200/JGO.2015.000786

Tsujimoto, T., Yamamoto, Y., Wasa, M., Takenaka, Y., Nakahara, S., Takagi, T., … Ito, T. (2015). 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. *Oncology Reports*, *33*(1), 33–39. https://doi.org/10.3892/or.2014.3564

Vidal-Casariego, A., Calleja-Fernández, A., Ballesteros-Pomar, M., & Cano-Rodríguez, I. (2013). Efficacy of glutamine in the prevention of oral mucositis and acute radiation-induced esophagitis: a retrospective study. *Nutrition and Cancer, 65*(3), 424–429. https://doi.org/10.1080/01635581.2013.765017

List of Excluded Articles:

- See Appendix 2 for list of excluded articles with reason for exclusion.

Step 3.

Step 3 of the Evidence Analysis Process involves individually appraising each research article that meets the project's inclusion criteria using the evidence worksheet template and quality criteria checklist, also called the Academy's risk of bias tool (Academy of Nutrition and Dietetics, 2016). The study design and process for each research study are assessed for quality in this step. This is completed by answering 4 questions on relevance and 10 questions on validity. Using the answers to these questions, a designation of negative (-), neutral (∅), or positive (+) quality is given to each study (Academy of Nutrition and Dietetics, 2016)**.** See Appendix 1 for the completed worksheets and checklists for each included study. The results from all studies are shown on the Tally Sheet found in Appendix 3.

Step 4.

In step four, the most important aspects of each study are organized into an overview table (Table 4, found in Chapter 4) including the author(s), study design, year, class rating, study type/purpose, study populations, intervention, outcomes, and limitations (Academy of Nutrition and Dietetics, 2016). Each study's results, and how the results relate to this project's research questions, are described in brief statements. Finally, an evidence summary is written that synthesizes all the research and details any themes. This summary includes an overall summary statement, comparison factors statements, methodological statements, outcome impact statements, and any definitions necessary (Academy of Nutrition and Dietetics, 2016).

Step 5.

A conclusion statement and a grade of strength for the available evidence is created in step five (Academy of Nutrition and Dietetics, 2016). There are five possible grades, listed below and detailed further in Figure 1.

- Grade I (good or strong): Studies have strong design and mostly consistent results without serious doubts. Large sample sizes are used in studies showing negative results.
- Grade II (fair): Studies have strong design but show inconsistency in results and some concerns due to limitations of the studies. Also, in this category would be evidence that comes only from weaker designed studies however with consistent results.
- Grade III (limited or weak): The evidence is from a small number of weakly designed studies. Studies with strong design either have not been done or are inconclusive due to study limitations.
- Grade IV (expert opinion): No research supports the conclusion; however, it is the opinion of informed medical professionals.

- Grade V (not assignable): There is no current available evidence to make a conclusion.

Conclusion Grading Table					
Strength of Evidence Elements	**Grades**				
	I Good/Strong	**II Fair**	**III Limited/Weak**	**IV Expert Opinion Only**	**V Grade Not Assignable**
Quality • Scientific rigor/validity • Considers design and execution	Studies of strong design for question Free from design flaws, bias and execution problems	Studies of strong design for question with minor methodological concerns, OR Only studies of weaker study design for question	Studies of weak design for answering the question OR Inconclusive findings due to design flaws, bias or execution problems	No studies available Conclusion based on usual practice, expert consensus, clinical experience, opinion, or extrapolation from basic research	No evidence that pertains to question being addressed
Consistency Of findings across studies	Findings generally consistent in direction and size of effect or degree of association, and statistical significance with minor exceptions at most	Inconsistency among results of studies with strong design, OR Consistency with minor exceptions across studies of weaker design	Unexplained inconsistency among results from different studies OR single study unconfirmed by other studies	Conclusion supported solely by statements of informed nutrition or medical commentators	NA
Quantity • Number of studies • Number of subjects in studies	One to several good quality studies Large number of subjects studied Studies with negative results have sufficiently large sample size for adequate statistical power	Several studies by independent investigators Doubts about adequacy of sample size to avoid Type I and Type II error	Limited number of studies Low number of subjects studied and/or inadequate sample size within studies	Unsubstantiated by published research studies	Relevant studies have not been done
Clinical impact • Importance of studied outcomes • Magnitude of effect	Studied outcome relates directly to the question Size of effect is clinically meaningful Significant (statistical) difference is large	Some doubt about the statistical or clinical significance of the effect	Studied outcome is an intermediate outcome or surrogate for the true outcome of interest OR Size of effect is small or lacks statistical and/or clinical significance	Objective data unavailable	Indicates area for future research
Generalizability To population of interest	Studied population, intervention and outcomes are free from serious doubts about generalizability	Minor doubts about generalizability	Serious doubts about generalizability due to narrow or different study population, intervention or outcomes studied	Generalizability limited to scope of experience	NA

Figure 1. Conclusion Grading Table. This figure explains the five possible grades of strength of evidence (Academy of Nutrition and Dietetics, 2016).

Summary

The Evidence Analysis Process Method is a detailed, well-respected, multiple step process of critically analyzing nutrition research. The next chapter in this project discusses each study that was included in this review, presents a quality rating for each study, and ends with a conclusion statement with a grading of the evidence. Chapter 5 will include the evidence summary and applications to clinical practice.

Chapter 4: Results

Types and Order of Included Studies

A total of ten studies met inclusion criteria and were included in this evidence analysis that examines the effect of oral glutamine on OM in head and neck cancer patients undergoing RT. Eight had conclusions that supported the use of oral glutamine supplementation, and two did not. Two of the studies with positive results were retrospective studies, five were randomized controlled trials, and one was a prospective cohort study. The two studies that did not show significantly positive evidence were randomized controlled trials. In this chapter each study will be reviewed including design, outcomes, strengths, and limitations. Additionally, each study's grade of strength will be presented, which was determined from the corresponding evidence worksheet and quality criteria checklist (Appendix 1). Studies with positive results are presented first, followed by those with negative results. Additionally, studies are ordered from weakest to strongest study design. Table 4 shows selected data, outcomes and limitations of included studies.

Evidence for Oral Glutamine Supplementation in Head and Neck Cancer

Vidal-Casariego, Calleja-Fernandez, Ballesteros-Pomar & Cano-Rodriguez, 2013 – Neutral Rating

Vidal-Casariego et al. completed a retrospective study to determine if oral glutamine supplementation prevents OM or RT-induced radiation esophagitis, decreases the severity of either, helps maintain nutrition status, and/or decreases RT treatment interruptions (Vidal-Casariego, Calleja-Fernandez, Ballesteros-Pomar & Cano-Rodriguez, 2013). They evaluated 79 individuals with tumors of the head and neck (78 with HNC and 1 with melanoma)

and 38 patients with tumors in the chest area (29 with lung cancer, 6 with esophageal cancer and 3 with lymphoma). The intervention examined was 30 grams of glutamine, taken orally each day. The intervention cohort was further split into two groups, one who started the supplement "early" (initiated before and continuing throughout RT), and the other who started the supplement in a "delayed" fashion (started after RT initiated due to late referral to the Nutrition department).

Almost half of the HNC patients received the glutamine in a "delayed" fashion (43%), about a third received it "early" (34.2%), and the last 22.8% did not receive any glutamine (Vidal-Casariego, Calleja-Fernandez, Ballesteros-Pomar & Cano-Rodriguez, 2013). The HNC patient cohort received RT at a median dose of 65 (60-70) Gy over 33 sessions. 62% of these patients received chemotherapy in addition to the RT (chemotherapy agents/regimens were not specified). Researchers reported that in the incidence of mucositis was lower in the glutamine groups compared to the no glutamine group (risk difference of developing OM was -9%, 95% CI). Additionally, OM was significantly less severe (p=0.039) in the group that received the early glutamine supplementation. Significantly less weight loss during RT was noted in the group that received "early" glutamine (-6.6%) compared to the "delayed" glutamine group (-11.3%) and the no intervention group (-13.4%) (p=0.009). Significantly more patients in the no treatment group required tube feeding than in the "delayed" group or in the "early" group (23.5%, 2.9% and 0.0%, respectively; p=0.04). No association was found between glutamine supplementation and the number of RT treatment interruptions.

In the RT-induced esophagitis cohort of patients, RT treatment was completed over 22-30 sessions of 42-60 Gy (Vidal-Casariego, Calleja-Fernandez, Ballesteros-Pomar & Cano-

Rodriguez, 2013). Over 97% of these patients received chemotherapy in addition to RT. 63.1% received “delayed” administration of glutamine, 23.7% received no glutamine, and only 13.2% received early glutamine. Researchers found that “early” use of glutamine was associated with decreased risk of esophagitis. Significantly fewer patients (P = 0.027) had a weight loss of more than 5% in either of the treatment groups compared to the no intervention group.

Based on their results, the researchers concluded that glutamine use was associated with significant reduction in the risk and severity of OM, weight loss, and tube feeding use (Vidal-Casariego, Calleja-Fernandez, Ballesteros-Pomar & Cano-Rodriguez, 2013). They also concluded that glutamine use was associated with significantly decreased risk of RT-induced esophagitis.

Strengths of this study include that it examined two different intervention times for the glutamine supplementation. Additionally, it examined nutritional status for each group, which can be a confounding factor to the development of OM. However, other confounding factors could not be controlled for given the retrospective nature of the study, including alcohol and tobacco use. Also, given the retrospective design, only correlation could be determined, and not causation. Additionally, convenience sampling was used which limits the applicability to the general population.

Akmansu, Iren & Gunturkin, 2018 – Neutral Rating

Akmansu, Iren, and Gunturkun also completed a retrospective study of HNC patients, with the aim of the research being to determine the relationships between glutamine supplementation and intensity and duration of OM, and on proinflammatory cytokines (Akmansu, Iren & Gunturkin, 2018). Their study, completed in Turkey, involved twenty-eight

patients with cancers of either the nasopharynx, larynx, oropharynx, or hypopharynx, all who received RT with or without chemotherapy (various agents and regimens). Eighteen of the twenty-eight patients received the intervention of powdered glutamine, 10 grams taken orally every 8 hours, mixed with water or fruit juice, from the first to last day of RT. Serum IL-1 beta, I-6, and TNF-alpha levels were measured at baseline, during the treatment and at conclusion of the cancer treatment.

The researchers found a significantly lower incidence of severe mucositis (grade 3 or worse) in the group receiving the glutamine supplementation (p=0.008). Those in the glutamine group also had significantly longer time to onset of OM (p=0.007). Further, OM occurred at a significantly higher median RT dose in the glutamine group than in the non-glutamine group (p=0.006). All 10 individuals in the non-intervention group experienced grade 2 or worse mucositis. 9 of the 18 individuals in the intervention group experienced grade 2 or worse mucositis, but the other 9 experienced grade 1 or no mucositis. The serum pro-inflammatory levels measured showed no significant differences. The authors concluded that glutamine supplementation was well tolerated, has proven effects on OM, and should be investigated further for its possible effects on inflammation (Akmansu, Iren & Gunturkin, 2018).

This study was small and retrospective, thus having similar limitations to the previous study by Vidal-Cassariego et al. Convenience sampling was used, and confounding factors could not be controlled for. It did maintain a consistent intervention of dosage and frequency of glutamine.

Pachon Ibanez et al., 2018 – Neutral Rating

Pachon Ibanez et al. completed a prospective cohort study that included 262 HNC patients with stage I-IV cancers of the oral cavity, oropharynx, supraglottis, glottis, nasopharynx, hypopharynx, or paranasal sinuses (Pachon Ibanez et al., 2018). Researchers sought to evaluate the relationship between incidence of OM and oral glutamine supplementation, with secondary objectives of determining incidence of odynophagia, cancer treatment interruptions, need for analgesia and nasogastric tubes. The intervention for this study was a dosage of 10 grams of glutamine, taken orally every 8 hours throughout RT by patients in the treatment group. The control group received nothing. Twenty-five percent of the glutamine group and 21% of the control group received only RT. The other participants received either chemotherapy, surgery, or a monoclonal antibody drug (Cetuximab) in addition to RT, though no significant differences between groups were noted. The length of the intervention was not specified. Seventy Gy given in 2 Gy/day radiation sessions was used for all patients, and chemotherapy agent and dosing varied for those it was used for. It was not stated how it was verified that all doses of glutamine were taken.

Researchers found that those not receiving the glutamine had a relative risk (RR) of developing mucositis of 1.78 (95% CI, p=0.047) in comparison to the group receiving the supplement (Pachon Ibanez et al., 2018). The intervention group also showed a significantly decreased need for nasogastric tube feeding (p=0.02), cancer treatment discontinuation (p=0.002), and prescriptions for analgesia (p=0.03). Multivariate analysis found two variables associated with the incidence of OM: tumor location and glutamine supplementation. Malignancies of the oral cavity were associated with a significantly higher incidence of mucositis than cancers of the supraglottis, glottis, or hypopharynx. Odynophagia was present in

significantly more participants in the control group versus the intervention group (77.9% versus 55.7%, p= 0.0001). The glutamine group had significantly less incidence of grade III-IV (severe) odynophagia (12.2% versus 42.7% of the control group, p <0.0001). Multivariate analysis found that tumor location, glutamine supplementation, and chemotherapy use were all associated with incidence of odynophagia. Researchers concluded that oral glutamine significantly decreased incidence of OM, as well as incidence and severity of odynophagia.

Strengths of this study included the large sample size, prospective nature and similarity between intervention and control groups. However, it was not randomized or blinded. Additionally, potential confounding factors such as nutrition status throughout cancer treatment, antibiotic use, and oral hygiene practices were not controlled for. Finally, participants in this study may have also received glutamine in enteral nutrition during the study period whether they were in the intervention group or not, as this type of supplemented formula was initiated for HNC patients at the specific institution sometime during the study period. Overall, the positive results of this study support the need for additional, larger, randomized, double-blinded placebo-controlled trials to provide stronger evidence for oral glutamine use in HNC.

E. Huang et al., 2000 – Positive Rating

A small, single-blind, placebo-controlled trial was completed in Taiwan by E. Huang et al. that evaluated the effect of oral glutamine supplementation on OM in 17 patients with HNC of the nasopharynx, oropharynx, or oral cavity (E. Huang, 2000). Patients received the same RT treatment of 25 fractions of 1.8 Gy/fraction, five days per week, with no other cancer treatments during the study. Patients were instructed to swish and then spit out 2 grams of

glutamine powder in 30 ml of normal saline, four times per day, throughout their RT treatment. It was not stated if compliance to the intervention was measured. Researchers found a significantly less severe and significantly shorter duration of objective OM in the glutamine group (p=0.006), as well as significantly shorter time of duration of subjective grade 3 or higher (severe) OM (p=0.0386). Researchers concluded that severity and duration of objective OM may be significantly reduced by oral glutamine supplementation.

Strengths of this study include its placebo controlled, RCT design, and that it controlled for weight change during the trial, betel nut, tobacco, and alcohol use, and use of prophylactic drugs or other mouthwashes. Additionally, all patients received the same RT treatment during the study, and chemotherapy was not used. Weaknesses include that the sample size was very small, was completed at only one institution, and was only single-blinded. Additionally, oral hygiene practices were not controlled for. Despite these weaknesses, the positive results warrant further study in larger well-controlled trials.

Chattopadhyay et al., 2014 – Neutral Rating

Chattopadhyay et al. completed an RCT in India of 70 HNC patients with stage I-IV cancers of the oral cavity, larynx, hypopharynx, nasopharynx, or oropharynx who underwent RT with or without chemotherapy (Chattopadhyay, Saha, Azam, Mukherjee & Sur, 2014). Participants received external beam RT at 2 Gy/fraction. Researchers sought to compare the effect of oral glutamine supplementation on OM. This study utilized an intervention of 10 grams of glutamine powder suspended in 1000 mL of water which was swished and swallowed daily on cancer treatment days (five days per week) 2 hours before the start of treatment.

Researchers included patients who were able to take in an average 800 of the 1000 ml of solution. The length of cancer treatment was not specified; however, it was individualized as researchers stopped the RT when grade III or IV mucositis developed.

Researchers found that the intervention group had significantly less frequent grade III OM ($p=0.02$) and grade IV OM ($p=0.04$), significantly longer time to onset of OM ($p<0.001$) and significantly shorter duration of severe (grade III or worse) OM ($p<0.001$) (Chattopadhyay, Saha, Azam, Mukherjee & Sur, 2014). However, when analyzed by treatment, patients receiving only RT and taking glutamine did not experience a statistically significant difference in severity of OM in comparison to those not taking glutamine. In contrast, those in the intervention group who received chemotherapy and RT experienced significantly less severe (grade III or IV) OM than those in the control group receiving both chemotherapy and RT ($p = 0.03$ for grade III OM and $p = 0.02$ for grade IV OM). In their conclusion, researchers acknowledged their positive findings while cautioning the need for future studies with larger samples prior to glutamine becoming standard treatment protocol.

A strength of this study is its design as a RCT, as well as the similarities in groups in several areas including age, sex, tumor location, stage of disease, treatment provided, and RT treatment sites. Weaknesses of this study were the lack of blinding, the fairly small sample size, and that potential confounding factors such as suboptimal oral hygiene, lower than average nutritional status, no antibiotic use or other prophylactic agent use early in OM, and alcohol and tobacco use were not evaluated between groups. Additionally, this was a single institution study, thus limiting applicability of results to the broader population. Despite these

weaknesses, this trial gives good evidence for use of an oral glutamine suspension in HNC patients undergoing RT, and justifies the need for further larger, blinded, trials.

Pathak et al., 2019 – Neutral Rating

Pathak et al. completed an RCT in India of 56 HNC patients with stage III-IV oropharynx or larynx cancer (Pathak, Soni, Sharma, Patni & Gupta, 2019). The researchers sought to examine the role and efficacy of oral glutamine supplementation on OM and dysphagia in these patients while they underwent concurrent chemoradiation. Time to onset of OM and dysphagia, incidence of treatment interruptions (defined as more than three RT sessions missed in a row), and significant weight reduction (defined as more than 3 kilograms from the beginning of the study) were secondary objectives. All participants received 70 Gy in 35 fractions and concurrent cisplatin consisting of weekly injection doses based on body surface area. A dose of 10 grams of glutamine once per day, taken orally (or through feeding tube if needed), throughout each participant's 7-week cancer treatment was prescribed. The glutamine was only taken on RT treatment days (five days per week). The researchers did not state how it was verified that the glutamine was ingested.

The results showed significantly less severe OM in the group who received the glutamine at the seventh week of treatment ($p< 0.001$), as well as significantly longer time to onset of these symptoms (Pathak, Soni, Sharma, Patni & Gupta, 2019). They also found that the treatment group had less severe dysphagia and a longer time to onset of dysphagia (p values < 0.05 assessed at weeks 2, 4, 6, and 7 of treatment). Finally, the treatment group had significantly less participants who experienced weight loss ($p=0.004$), significantly less

treatment interruptions (p=0.025), need for nasogastric tube feeding (p=0.03), and incidence of severe toxicity (need for hospital admission, p=0.03). The research team acknowledged the need for larger, multicentric, double-blinded studies on oral glutamine to prove their findings.

Strengths of this study include that it was a randomized controlled trial and that the patients received the exact same cancer treatment in both groups. The study also had an adequate number of participants complete the protocol to allow for the researcher's goal of eighty percent study power (23 participants in each study arm). However, the study was not blinded, did not have a placebo, and still had a rather small sample size located in only one geographical area (at one hospital). Finally, the study did not assess for possible confounding factors such as BMI, nutrition status of patients at baseline (other than patients being "appropriate for treatment"), tobacco use, oral hygiene care adequacy, or use of antibiotics for OM. Overall this RCT contributes to the evidence for considering use of oral glutamine for this population, and given this study's limitations, the need for further larger, blinded, placebo-controlled trials with better control of possible confounding factors.

Pattanayak et al., 2016 – Neutral Rating

Pattanayak et al. completed an RCT in India in 2016 with 162 HNC patients with stage II-IV cancers of the oral cavity, oropharynx, hypopharynx, larynx, or nasopharynx (Pattanayak, Panda, Dash Mohanty & Samantaray, 2016). The investigators' aim was to examine the efficacy and safety of oral glutamine supplementation on HNC patients undergoing chemoradiation over seven weeks. All participants received the exact same cancer treatment regimens, however the length of treatment varied due to tolerance of therapy. Treatment consisted of

concurrent chemotherapy (weekly cisplatin with dosing based on body surface area) and a goal of 70 Gy external-beam RT given in 35 fractions using a shrinking field technique. The intervention in this group was similar to that of Chattopadhyay et al. in that the participants were instructed to swish and swallow the glutamine suspended in water. The dose in this trial was slightly higher at 15 grams given twice per day throughout treatment, each time given in a glass of water. The authors did not state how it was verified that each dose was consumed.

Researchers found that the glutamine supplementation significantly decreases severity of and delayed time to onset of OM ($p<0.05$) (Pattanayak, Panda, Dash Mohanty & Samantaray, 2016). Additionally, they reported that adverse events such as pain, dysphagia, nausea, edema, and cough were significantly more common in the control group than in the intervention group. Researchers concluded that oral glutamine is a feasible and affordable treatment for OM.

Strengths of this study include its RCT design, fairly large sample size, inclusion of tobacco and betel nut use when comparing the control and intervention groups, and standardized cancer treatments between the two groups. However, the study was not blinded and did not assess for other possible confounding factors such as suboptimal oral hygiene, lower than average nutritional status/changes to nutritional status throughout the study, or antibiotic or other prophylactic use early in OM. Additionally, some participants did not complete all weeks of cisplatin treatment, and it was not specified whether this was different between groups. Despite these limitations, this RCT contributes good evidence for the consideration of the use of an oral glutamine swish and swallow in this patient population, and necessitates the need for blinded, larger trials.

Tsujimoto et al., 2015 – Positive rating

A double-blind, randomized, placebo-controlled trial was completed in Japan by Tsujimoto et al. in 2015 with 40 HNC patients with stage II-IV cancers of the nasopharynx, oropharynx, hypopharynx, or larynx (Tsujimoto et al., 2015). The aim of the study was to evaluate if glutamine decreases the severity of OM, as well as mucositis of the pharynx and larynx, for patients undergoing a standardized treatment of 6 weeks of chemotherapy and radiation. Secondary objectives were to determine duration and time to onset of mucositis, pain, incidence and duration of opioid use, total opioid dose, need for and duration of nutritional supplementation via feeding tube or peripheral parenteral nutrition, and clinical data. Patients received 66 or 70 Gy at 2 Gy/fraction, through five fractions per week. Chemotherapy treatment consisted of cisplatin and docetzel, both dosed based on body surface area. An intervention of 10 grams of glutamine, taken orally (or through a feeding tube if needed), three times per day (at 7:00, 11:00, and 16:00) throughout cancer treatment was given to the treatment group; the control group received 10 grams of a placebo three times per day. The researchers did not specify how it was verified that the patients received all required doses, but they indicated a compliance rate of 99.6%, as measured by a pharmacist.

The researchers found that glutamine significantly decreased the maximal mucositis grade (severity) (intervention group, 2.9+/-0.3; placebo group, 3.3+/-0.4; p=0.005) (Tsujimoto et al., 2015). No significant differences were found in time to onset of mucositis, duration of mucositis, or mean time to onset of severe mucositis. The average mucositis grade was significantly higher in the placebo group at weeks 5 and 6 (p=0.027, p=0.002, respectively).

During weeks 4, 5 and 6, pain scores were significantly lower in the intervention group than in the placebo group (p=0.049, p=0.019, p=0.032, respectively). Additionally, the average length of time opioids were used was significantly longer in the placebo group than in the intervention group (p=0.029). No significant difference in average total opioid dose was found between the two groups. The average length of time that nutrition supplementation was needed was significantly longer in the placebo group compared to the intervention group (p=0.046). No significant changes in average BMI or total daily caloric intake were reported. The intervention group had an average weight change of -3.6% from baseline to week 8, in comparison to a change of -6.0% in the placebo group, though this was not significant. Researchers also noted that there was no significant difference between amino acid profiles that were assessed from the intervention or placebo groups.

Researchers concluded that glutamine can significantly decrease chemoradiotherapy-induced mucositis severity in individuals with HNC. They also noted the importance of a multidisciplinary approach to care, stating that it can contribute to improved outcomes and improved patient quality of life.

This trial had significant strengths, including the design as a double-blinded, placebo-controlled RCT. Additionally, the intervention and control groups were very comparable, including standardized cancer treatment and no differences in BMI change, weight change and daily caloric intake between groups. The groups also had supervised oral hygiene care and assessment throughout the study by a nurse which is important as oral hygiene care adequacy is a known risk factor for mucositis. However, groups were not controlled for tobacco use.

Additionally, though oral hygiene was supervised throughout the treatment, the researchers did not specify if other prophylactic rinses or supplements were used by the participants. The sample size of this study was also fairly small. Still, this RCT contributes significantly to the evidence for consideration of use for oral glutamine in HNC patients. These results should be replicated in larger, well-controlled trials, ideally involving multiple institutions.

Evidence Against Oral Glutamine Supplementation in Head and Neck Cancer

C. Huang et al., 2019 – Positive Rating

C. Huang et al. studied 64 patients in Taiwan with stage I-IV HNC in their randomized, double-blinded, placebo-controlled trial. Most patients (65.6%) had oral cavity cancer, but diagnoses also included nasopharynx, oropharynx, hypopharynx, and larynx cancers (C. Huang et al., 2019). The aim of the study was to examine whether oral glutamine decreased OM and neck dermatitis while patients underwent intensity-modulated RT of 60-70 Gy total, given in 2 Gy fractions, with or without chemotherapy. Although the total number of individuals who did or did not receive chemotherapy did not differ significantly between groups, the type and frequency of chemotherapy may have, as this information was not provided in the study. Researchers reported that cisplatin or carboplatin were used, with or without the addition of 5-fluorouracil. Additionally, chemotherapy may have been given weekly or every 3 weeks depending on the patient. The intervention group took a self-administered dose of 10 grams of glutamine dissolved in cold water orally (or through a feeding tube if needed) three times per day before a meal starting 1 week before RT and ending 2 weeks after RT completion. The length of the treatment was not specified, and likely varied between patients given the RT and chemotherapy (if used) was individualized for the patient.

The researchers found a decreased mean maximum severity of mucositis in the treatment group compared with placebo; however, the difference was not significant (analysis of completers, p=0.169; PP multivariate analysis, p = 0.172) (C. Huang et al., 2019). The authors acknowledged that the higher percentage of participants with oral cavity cancer in their study (versus none in the study by Tsujimoto et al.) may have contributed to this result not being significant, since the oral mucosa tissue receives a higher amount of RT in these patients. The authors also did not find any significant difference in incidence or severity of dermatitis between the intervention and placebo group. According to the researchers, another important finding of the study was that a strong correlation was found between decrease in BMI and severity of OM when multivariate PP analysis was performed (p = 0.014), as they reported that this was the first study to show such a strong correlation. They concluded that further research is warranted on oral glutamine.

Strengths of this study include RCT design with doubling blinding and placebo control, assessment and similarity between groups of tobacco, alcohol and betel nut use, BMI, prognostic nutritional index, and daily caloric intake. Also, participants were not allowed to use any other nutritional supplements during the trial. However, weaknesses for this study include the fairly small sample size, the variety of chemotherapy agents as well as chemotherapy administration frequencies patients received, and the drop out of patients in the placebo arm due to an aversion to the placebo product, and the lack of assessment of antibiotic use, or oral hygiene care adequacy between groups. Also, there was no way to prove the protocol was followed by all patients, since the doses were self-administered. Further, seven patients did not complete RT, which the authors acknowledged could have affected randomization. The

researchers also noted that their study may have been underpowered, and that the high number of patients with oral cavity cancer may have contributed to the results, as this type of cancer involves more severe RT to the oral cavity, thus making it possible that worse OM could develop compared to the other cancer types. Of note, the study by Tsujimoto et al. (2015) that yielded a positive rating in this evidence analysis did not include any patients with oral cavity cancer. It Is also important to note that although the results of this study were not significant, they were still positive.

Lopez-Vaquero, Guitierrez-Bayard, Rodriguez-Ruiz, Saldana-Valderas, & Infante-Cossio, 2017 – Positive Rating

One other double-blind, placebo-controlled RCT was found that did not yield significantly positive results for oral glutamine supplementation (Lopez-Vaquero, Guitierrez-Bayard, Rodriguez-Ruiz, Saldana-Valderas, & Infante-Cossio, 2017). This study was completed in Spain and included forty-nine patients with HNC of the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx, who were randomized to either receive ten grams of oral glutamine dissolved in water three times daily with meals, or placebo (maltodextrin). Researchers sought to examine if the glutamine would reduce incidence or severity of OM and dermatitis when the patients underwent RT with or without chemotherapy for six weeks. Patients received 66 Gy or 70 Gy RT (depending on if a patient was post-surgical), dosed at 2 Gy/fraction. If chemotherapy was used cisplatin or cetuximab was administered, with dose based on body surface area. The researchers indicated that there were no significant differences between groups for cancer treatment regimens. A 100% compliance rate to the intervention was recorded by the main researcher, who also performed a count of bags used in the trial.

Outcomes of the study included that the researchers did not find a significant difference in incidence or severity of OM between groups, although the placebo group had higher values for both (Lopez-Vaquero, Guitierrez-Bayard, Rodriguez-Ruiz, Saldana-Valderas, & Infante-Cossio, 2017). Interestingly, they did find that the glutamine group had significantly less incidence and severity of dermatitis ($p=0.038$ and $p=0.032$, respectively). The authors of this study concluded that slight clinical effects in reducing OM were seen with the use of oral glutamine, though results were not significant. Additionally, benefit was seen in reducing incidence and severity of dermatitis, however more research is warranted on glutamine's use for both clinical symptoms.

Strengths of this study include its gold standard design as a double-blind, placebo-controlled RCT. Also, the study controlled for weight change, alcohol and tobacco use in participant groups, and cancer treatment. Additionally, intervention compliance measurement (100%) was completed. The weaknesses of this study include that it was completed at only one institution and had a fairly small sample size. Also, oral hygiene adequacy during treatment was not measured. Though this study did not find significant positive results for glutamine's impact on OM, the results did trend towards significance. As with all studies that have notable limitations, these studies necessitate the need for more well-designed research in this area.

Conclusion Statements

Incidence of Oral Mucositis - Grade: III (Limited)

Oral glutamine supplementation potentially decreases the incidence of OM in HNC patients undergoing RT. Of the ten studies included in this evidence analysis, two studies demonstrated a significant decrease in incidence of mucositis. One additional study reported

positive results although did not indicate if they were significant. Three studies reported no significant change in incidence of mucositis, and the final four studies did not report any results related to incidence of mucositis.

The two studies that showed significantly positive results were rated as neutral quality. The study with positive, though unclear if significant results was also rated as neutral quality. Two of the three studies without positive results had neutral quality ratings and one had positive quality rating. Of the four studies without a result on incidence of mucositis, two were positively rated and two were neutrally rated.

Severity of Oral Mucositis: Grade III (Limited)

Oral glutamine supplementation potentially decreases the severity of OM in HNC patients undergoing RT. Of the ten studies included in this evidence analysis, seven studies reported significant decrease in severity of mucositis with the use of oral glutamine supplementation. Two studies had positive results, although the results were not statistically significant. One study did not report on severity of mucositis.

Two of the seven studies that reported significant results were rated as positive quality, and the other five were neutral rated. One of the studies with positive but not significant results was of positive quality and the other was of neutral quality. The one study that did not report on severity of mucositis was of neutral quality.

Table 4. Overview Table

Author, Year, Study Design, Class, Rating	Study Purpose	Study Population	Intervention	Incidence of OM Outcomes	Severity of OM Outcomes	Other Outcomes	Limitations
Vidal-Casariego et al., 2013 Retrospective Cohort Study Class: B Rating: ∅	To determine if oral glutamine prevents OM or RT-induced radiation esophagitis, decreases the severity of either, helps maintain nutrition status, and/or decreases RT treatment interruptions	n=117 Inclusion: Individuals undergoing RT with or without chemotherapy, for tumors of the head and neck (78 with HNC and 1 with melanoma) or of the chest area (29 with lung cancer, 6 with esophageal cancer and 3 with lymphoma)	30 grams glutamine orally per day either early (before/during RT), or delayed (started after RT initiated), or no supplement given	Lower incidence of OM in the glutamine supplementation groups (risk difference of developing OM was -9%, 95% CI)	Significantly less severe OM in the group that received "early" glutamine supplementation (p=0.039)	Head and neck group: Significantly less weight loss during RT observed in the group that received "early" glutamine compared to the other groups (p=0.009) Significantly more patients in the no supplement group required tube feeding compared to the other two groups (p=0.04) Chest area group: "Early" use of glutamine was associated with decreased risk of esophagitis. Significantly fewer patients had weight loss of more than 5% in either treatment group compared to no supplement group (p = 0.027)	All possible confounding factors not controlled for given the retrospective nature Given the retrospective design, only correlation could be determined, and not causation. Convenience sampling was used which limits the applicability to the general population.

Akmansu et al., 2018 Retrospective Cohort Study Class: B Rating: ∅	To determine the relationships between glutamine supplementation and intensity and duration of OM, and on proinflammatory cytokines	n=28 Inclusion: Patients with cancers of either the nasopharynx, larynx, oropharynx, or hypopharynx, who received RT with or without chemotherapy	10 grams powdered glutamine taken orally mixed with water or fruit juice every 8 hours, from the first to last day of RT, versus no intervention	All 10 individuals in the non-intervention group experienced grade 2 or worse mucositis. 9 of the 18 individuals in the intervention group experienced grade 2 or worse mucositis. The other 9 experienced grade 1 or no mucositis	Significantly lower incidence of severe (grade 3 or worse) mucositis in the intervention group (p=0.008)	Significantly longer time to onset of OM in the intervention group (p=0.007) OM occurred at a significantly higher median RT dose in the glutamine group (p=0.006) No significant differences in serum pro-inflammatory levels	Small sample size Single institution study Confounding factors could not be controlled for Convenience sampling limits applicability to larger population Given the retrospective design, only correlation could be determined, and not causation

Pachon Ibanez et al., 2018 Prospective Cohort Study Class: B Rating: ∅	To evaluate the relationship between incidence of OM and oral glutamine supplementation, with secondary objectives of determining incidence of odynophagia, cancer treatment interruptions, need for analgesia and nasogastric tubes	n=262 patients Inclusion: Stage I-IV cancers of the oral cavity, oropharynx, supraglottis, glottis, nasopharynx, hypopharynx, or paranasal sinuses, undergoing RT with or without chemotherapy, surgery, or a monoclonal antibody drug, without any other prophylactic measures or mucositis at baseline	10 grams of glutamine taken every 8 hours throughout RT, versus no intervention in control group	Control group had RR of developing mucositis of 1.78 in comparison to intervention group (p=0.047)	N/A	Significantly decreased need for nasogastric tube feeding in intervention group (p= 0.02), cancer treatment discontinuation (p=0.002), and prescriptions for analgesia (p=0.03) Malignancies of oral cavity were associated with a significantly higher incidence of mucositis in comparison to the other included cancers Odynophagia present in significantly more individuals in control group (p=0.0001), control group also experienced significantly higher incidence of severe odynophagia (p<0.0001)	Not stated how compliance was verified Length of intervention not specified Sample size not large enough to complete multivariate analysis Not randomized Not blinded Potential confounding factors such as nutrition status throughout treatment, antibiotic use, and oral hygiene practices were not controlled for Participants may have also received glutamine in enteral nutrition during the study period whether or not they were in the intervention group

E. Huang et al., 2000 Randomized, single blind, placebo-controlled trial Class: A Rating: +	Evaluated the effect of oral glutamine supplementation on OM	n=17 Inclusion: HNC of the nasopharynx, oropharynx, or oral cavity, undergoing RT	Swish and spit out 2 grams of glutamine powder in 30 ml normal saline, four times per day, throughout RT	N/A	Significantly less severe objective OM in glutamine group (p=0.006)	Significantly shorter time of duration of subjective grade 3 or higher (severe OM) in the glutamine group (p=0.0386) No difference between analgesic drug use, mean body weight change	Sample size was very small Was completed at only one institution Only single-blinded Oral hygiene care adequacy not assessed

Chattopadhyay et al., 2014 Randomized controlled trial Class: A Rating: ∅	To compare the effect of oral glutamine supplementation on OM	N=70 Inclusion: Stage I-IV HNC of the oral cavity, larynx, hypopharynx, nasopharynx, or oropharynx, undergoing RT with or without chemotherapy, performance status of 50% or higher on Karnofsky performance scale	10 grams of glutamine powder suspended in 1000 ml of water, swished and swallowed daily on cancer treatment days 2 hours before treatment	When analyzed by cancer treatment, those in intervention group only receiving RT and not chemotherapy did not experience a statistically significant difference in incidence of OM compared to control group	Intervention group had significantly less frequent grade 3 ($p=0.02$) and grade 4 OM ($p=0.04$)	Intervention group had significantly longer time to onset of OM ($p<0.001$) and significantly shorter duration of severe (grade III or worse) OM ($p<0.001$) Those in the intervention group receiving chemotherapy had significantly less severe OM than the control group participants receiving chemotherapy.	No blinding Fairly small sample size Potential confounding factors such as suboptimal oral hygiene, lower than average nutritional status, no antibiotic use early in OM, and alcohol and tobacco use were not evaluated between groups Single institution study

Pathak et al., 2019 Randomized controlled trial Class: A Rating: ∅	Examine if oral glutamine supplementation decreases incidence or severity of OM or dysphagia Secondary objectives included time to onset of OM and dysphagia, incidence of treatment interruptions, and significant weigh reductions	N=56 Inclusion: Stage III-IV oropharynx or larynx cancer, undergoing concurrent chemoradiation	10 grams of glutamine taken orally once per day on treatment days, throughout 7-week cancer treatment	All experienced grade II OM or worse by the seventh week	Significantly less severe OM in intervention group at the seventh week of treatment ($p<0.001$)	Significantly longer time to onset of OM Intervention group had less severe dysphagia and a longer time to onset of dysphagia Intervention group had significantly less participants who experienced weight loss ($p=0.004$), significantly less treatment interruptions ($p=0.025$), need for nasogastric tube feeding ($p=0.03$), and incidence of severe toxicity ($p=0.03$)	Did not state how compliance was measured Not blinded Small sample size located in only one geographical area (at one hospital) Did not assess for possible confounding factors such as BMI, nutrition status of patients at baseline (other than patients being "appropriate for treatment"), tobacco use, oral hygiene care adequacy, or use of antibiotics for OM

Pattanayak et al., 2016 Randomized controlled trial Class: A Rating: ∅	To examine the efficacy and safety of oral glutamine supplementation on HNC patients undergoing chemoradiation	n= 162 Inclusion: HNC patients with stage II-IV cancer of the oral cavity, oropharynx, hypopharynx, larynx, or nasopharynx, who underwent chemoradiation	Swish and swallow 15 grams of glutamine suspended in a glass of water twice per day throughout treatment	N/A	Significantly decreased severity of OM in intervention group ($p<0.05$)	Significantly delayed time to onset of OM ($p<0.05$) Adverse events such as pain, dysphagia, nausea, edema, and cough were significantly more common in the control group than in the intervention group	Not blinded Did not state how compliance was measured Only conducted at a single institution in India Did not assess for other possible confounding factors such as suboptimal oral hygiene, lower than average nutritional status, or no antibiotic use early in OM Not all patients received all of chemotherapy regimens, and it was not specified whether this was different between groups.

Tsujimoto et al., 2015 Randomized controlled trial Class: A Rating: +	To evaluate if glutamine decreases the severity of OM, as well as mucositis of the pharynx and larynx Secondary objectives were to determine duration and time to onset of mucositis, pain, incidence and duration of opioid use, total opioid use, need for and duration of nutritional supplementation via feeding tube or peripheral parenteral nutrition, and clinical data	N= 40 Inclusion: HNC patients with stage II-IV cancers of the nasopharynx, oropharynx, hypopharynx, or larynx, undergoing chemoradiation for 6 weeks (uniform treatment for all patients)	10 grams of glutamine, taken orally three times per day throughout cancer treatment, or 10 grams of placebo three times per day	N/A	Significantly decreased mean maximal mucositis grade in the intervention group (p=0.005)	No significant differences in time to onset of mucositis, duration, or mean time to onset of severe mucositis Average mucositis grade was significantly higher in the placebo group at weeks 5 and 6 Pain scores were significantly lower in the intervention group during weeks 4, 5 and 6 Average length of time opioids were used was significantly longer in placebo group Average length of time nutrition supplementation needed was significantly longer in placebo group	Compliance rate was high however did not specify how this was measured Groups were not controlled for tobacco use Not specified if other prophylactic rinses or supplements could be or were used by the participants Sample size was small Single institution study

C. Huang et al., 2019 Randomized controlled trial Class: A Rating: ∅	To examine whether oral glutamine decreased OM and neck dermatitis while patients underwent intensity-modulated RT with or without chemotherapy	N=64 Inclusion: HNC patients with stage I-IV HNC, most with oral cavity cancer (65.6%), but also could have nasopharynx, oropharynx, hypopharynx, or larynx cancers	10 grams of glutamine dissolved in cold water three times per day before a meal starting 1 week before RT and ending 2 weeks after RT completion	N/A	Decreased mean maximum severity of mucositis in intervention group, however not significant	No significant difference in incidence or severity of dermatitis Strong correlation found between decrease in BMI and severity of OM	Type and frequency of chemotherapy may have differed between groups as this was not specified by researchers Fairly small sample size Single institution study Drop out of patients in the placebo arm due to aversion of the placebo product Lack of assessment of antibiotic use, or oral hygiene care adequacy between groups No way to prove the protocol was followed by all patients, since the doses were self-administered Seven patients did not complete RT, which the authors acknowledged could have affected randomization Study may have been underpowered, and high number of patients with oral cavity cancer may have contributed to the results, as this type of cancer involves more severe RT to the oral cavity, thus making it possible that worse OM could develop compared to the other cancer types.

Lopez-Vaquero et al., 2017 Randomized controlled trial Class: A Rating: +	To examine if glutamine supplementation would reduce incidence or severity of OM and dermatitis	N=49 Inclusion: HNC patients with cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx, underwent RT with or without chemotherapy for 6 weeks	Ten grams of glutamine dissolved in water three times per day with meals or placebo (maltodextrin)	No significant difference in incidence of OM, although placebo group had higher values	No significant difference in severity of OM, although the placebo group had higher values	Intervention group had significantly less incidence and severity of neck dermatitis	Completed at only one institution Fairly small sample size Oral hygiene adequacy during treatment was not measured.

Chapter 5: Discussion

This evidence analysis examined the possible effect of oral glutamine supplementation on RT-induced OM in HNC patients undergoing RT. The evidence reviewed found that oral glutamine potentially decreases the incidence and severity of OM in this population.

Two studies, both rated as neutral quality, found that incidence of OM was significantly decreased with use of glutamine (Pachon Ibanez et al., 2018; Vidal-Casariego et al., 2013). One additional neutral-rated study reported positive results however did not say whether findings were significant (Akmansu et al., 2018). Three studies found no significant difference in incidence of OM with use of glutamine (Chattopadhyay et al., 2014; Lopez-Vaquero et al., 2017; Pathak et al., 2019). Of these, one was positive quality (Lopez-Vaquero et al., 2017) and two were neutral quality (Chattopadhyay et al., 2014; Pathak et al., 2019).

Seven studies reported a significant decrease in severity of mucositis with the use of glutamine (Akmansu et al., 2018; Chattopadhyay et al., 2014; E. Huang et al., 2000; Pathak et al., 2019; Pattanayak et al., 2016; Tsujimoto et al., 2015; Vidal-Casariego et al., 2013). Two of these were positive quality (E. Huang et al., 2000; Tsujimoto et al., 2015) and five were neutral quality (Akmansu et al., 2018; Chattopadhyay et al., 2014; Pathak et al., 2019; Pattanayak et al., 2016; Vidal-Casariego et al., 2013). Two other studies reported positive, though insignificant results. (C. Huang et al., 2019; Lopez-Vaquero et al., 2017). One was neutral quality (C. Huang et al., 2019) and one was positive quality (Lopez-Vaquero et al., 2017).

Similarities in the Research

A similarity in the research was that all studies were conducted at single institutions, which limits the generalizability of the results and highlights the need for multi-center trials to

be competed in the future. Additionally, the supplementation time frame always included the entire course of RT for at least one of the intervention groups in each study. Vidal-Casariego et al. (2013) had a group that started the supplement after RT had already initiated, but this was not intentional and was a result of the retrospective nature of the study. All but two studies (Vidal-Casariego et al., 2013; C. Huang et al., 2019) had interventions that started and ended at the same time as the cancer treatments. Interestingly, the single RCT with glutamine supplementation that started 1 week before and continued 2 weeks after cancer treatment completion showed no significant results (C. Huang et al., 2019). In contrast, the retrospective trial by Vidal-Casariego et al. (2013) found positive results for their "early" group that received glutamine supplementation prior to the start of their RT (and continued throughout RT).

Another similarity in the research was that no adverse effects were reported in any study. Thus, oral glutamine does appear to be a safe supplement for this population.

Inconsistencies in the Research

There were numerous inconsistencies in the research, including glutamine dosing. Positive results were seen with dosages of 8, 10 or 30 total grams total per day, given once or up to four times each day, via a swish and swallow method, swish and spit method, or just "consuming" orally. The pilot trial from the year 2000 used the lowest dose of 2 grams given four times per day for a total of 8 grams, and had positive results (E. Huang et al., 2000). Two trials with positive results used doses of 10 grams per day (Chattopadhyay et al., 2014; Pathak et al., 2019). A total dose of 30 grams per day, given orally, was used in five trials with positive results (Pachon Ibanez et al., 2018; Pattanayak et al., 2016; Tsujimoto et al., 2015; Akmansu et

al., 2018; Vidal-Casariego et al., 2013), and in two trials with negative results (C. Huang et al., 2019; Lopez-Vaquero et al., 2017).

Glutamine administration also varied in the research. Two studies had participants swish and swallow the glutamine (Chattopadhyay et al., 2014; Pattanayak et al., 2016), and one study had participants just swish and spit the glutamine out (E. Huang et al., 2000). The seven other studies only listed that the glutamine was to be consumed orally unless administration via tube feeding was needed, if specified. Tsujimoto et al. (2015) had a significant number of patients that required feeding tubes during the study, 16 out of their 20 patients in the treatment group. As this trial found significant results, it does not appear that the glutamine coming in direct contact with the oral mucosa is needed for the intervention to be effective. As previously discussed in chapter 2 good oral care is recommended for treating oral mucositis, thus perhaps the act of swishing a solution in the mouth provides hygienic benefits rather than any benefit related specifically to the glutamine. This could have contributed to the positive results found by E. Huang et al. (2000) when participants swished and spit the glutamine solution four times per day.

Patient compliance to study protocols was also inconsistently measured in the studies reviewed. Only three studies stated that patient compliance with the regimens was measured. Chattopadhyay et al. (2014) indicated that an average consumption of at least 800 ml of the 1000 ml solution needed to be consumed in order to be included in the study. Tsujimoto et al. (2015) reported a compliance rat of 99.6% which was monitored by a pharmacist, though researchers did not specify how this was done. Lopez-Vaquero et al. (2017) indicated that patient non-compliance was documented, though like the study by Tsujimoto et al. (2015) it

wasn't clear how monitoring was done. Future studies should ensure that verification of dose ingestion is in each study protocol and specifically state this, as well as compliance rates, in the published report.

In addition to variability in verification of treatment adherence, the assessment and control of the arms of each individual study also varied considerably. Multiple lifestyle factors can contribute to the risk of severe mucositis, only some of which each study chose to evaluate. Tobacco use was only controlled for in five studies (C. Huang et al., 2019; E. Huang et al., 2000; Lopez-Vaquero et al., 2017; Pachon Ibanez et al., 2018; Pattanayak et al., 2016;). Alcohol use was only controlled for in four studies (C. Huang et al. 2019; E. Huang et al., 2000; Lopez-Vaquero et al., 2017; Pattanayak et al., 2016). Betel nut chewing was only controlled for in three studies (Pattanayak et al., 2016; C. Huang et al., 2019; E. Huang et al., 2000). Future studies should all control for alcohol, tobacco and betel nut use, given the possible contribution to risk of OM with these behaviors.

Another inconsistency and weakness of the entire body of evidence is that overall glutamine intake and status was not measured. Intake of glutamine would be clinically difficult to monitor in the outpatient setting given ad lib diets without oversight; however, an effort could be made to assess this. Additionally, no standard way of measuring body glutamine stores is recognized as accurate, which limits the ability to determine possible glutamine deficiency (Cruzat, Rogero, Keane, Curi & Newsholme, 2018). Nonetheless, glutamine intake and status could influence the impact that supplemental glutamine has on individuals and is therefore a weakness of this area of research.

As mentioned in chapter 2, lower than average nutritional status can also contribute to risk for OM (Luo et al., 2005). Poor nutritional status can also impair healing capabilities which are needed once mucositis is present (C. Huang et al, 2019). Further, it is plausible that poor nutritional status at baseline would indicate a higher risk for glutamine deficiency which could influence how effective glutamine supplementation is for an individual. Given all these factors, nutritional status should be assessed and monitored throughout every trial, however the current research did not do this consistently. Two studies did not control for any nutritional factors (Chattopadhyay et al., 2014; Pattanayak et al., 2016). One study only examined nutritional status at baseline but not throughout the study (Pachon Ibanez et al., 2018), and one only examined weight change during the study but not baseline BMI or nutritional status (Pathak et al., 2019). This is a significant limitation for these four studies and is highlighted by the finding by C. Huang et al. (2019) of a significant association between decline in BMI during treatment and severity of mucositis. Interestingly, one study by Akmansu et al. (2018) did not find an association between change in weight status, percent of weight change, or BMI. Nevertheless, future researchers should strongly consider controlling for baseline nutrition status and monitoring it throughout their trial as it could contribute to OM risk.

Another inconsistency in the research is the mention of and control of possible other OM treatments being used by participants. E. Huang et al. (2000) specifically mentioned that individuals were excluded if they used prophylactic drugs or mouthwashes besides the glutamine intervention, however no other studies mentioned this.

Blinding was inconsistent across studies as well. Three of the eight prospective studies included were double-blinded (Tsujimoto et al., 2015; Huang et al., 2019; Lopez-Vaquero et al.,

2017). One study, by Huang et al. (2000), was only considered to be single-blinded. The inclusion of double blinding in studies that did not have this control could have potentially affected outcomes. Individuals who knew they were receiving the intervention may have been more motivated to do well, and perhaps then ate better during the treatment or adhered to better oral hygiene care regimens. Also, the medical staff assessing the mucositis may have been biased towards finding positive results in those individuals who received the treatment.

Another inconsistency in the current research is the types of HNC included in the studies. C. Huang et al. examined mostly (65.6%) oral cavity cancer patients (2019) and did not find significantly positive results for the use of oral glutamine. The researchers reported that the high prevalence of oral cavity cancer in their study could have contributed to why their results were not significant, since higher RT directed specifically towards the oral cavity for those cancers could contribute to a higher risk for OM (C. Huang et al., 2019). Also, in the multivariate analysis completed by Pachon Ibanez et al. (2018), tumor localization to the oral cavity was the only other factor besides lack of glutamine use that increased relative risk (RR) of OM in their study. Given this possibility of higher risk of OM with oral cavity cancer, larger studies with groups of various HNC types should be completed, with sub-group analysis for each cancer type.

Finally, cancer treatment types varied in the studies reviewed; only four of the ten studies used standardized cancer treatment types and doses for all participants (Tsujimoto et al., 2015; Pattanayak et al., 2016; Pathak et al., 2019; E. Huang et al., 2000). Chemotherapy and RT can both cause OM, thus it is possible that the differences in treatment combinations could contribute to individual study outcomes. Ideally, cancer treatment type should be standardized

in each future study. Alternately, cohort size should be adequate so that subgroup analysis should be completed for various types and combinations of cancer treatments.

Conclusion and Application for Future Practice

Currently, there is limited evidence to support the use of oral glutamine to reduce incidence or severity of RT-induced OM in HNC patients. Though most studies (eight included in this review) were found to have significantly positive results, only two of those studies were determined to have a positive quality rating. In contrast, two studies did not produce significantly positive results, one of which was positively rated and one which was rated as neutral. This necessitates the need for further, well controlled trials before a strong conclusion regarding the routine use of this supplement for the HNC population can be made.

The field of supportive HNC care needs more evidence from larger, multi-center, double-blinded, randomized, well-controlled trials, to increase the body of evidence for or against oral glutamine supplementation. These studies should control for cancer treatment (types, doses, frequencies and length), tobacco, alcohol, and betel nut use, oral hygiene care adequacy at baseline and throughout the study, nutrition status at baseline and throughout the study, cancer type, and any concurrent mucositis treatments (such as antibiotics or other drugs) used.

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Appendix 1 Evidence Analysis Worksheets and Quality Criteria Checklists

Citation	Vidal-Casariego, A., Calleja-Fernández, A., Ballesteros-Pomar, M., & Cano-Rodríguez, I. (2013). Efficacy of glutamine in the prevention of oral mucositis and acute radiation-induced esophagitis: a retrospective study. Nutrition and Cancer, 65(3), 424–429. https://doi.org/10.1080/01635581.2013.765017
Study Design	Retrospective Cohort Study
Class	B
Quality Rating	∅ (neutral)
Research Purpose	• Determine if oral glutamine prevents RT-induced OM or esophagitis, decreases the severity of either, helps maintain nutrition status, and/or decreases RT treatment interruptions
Inclusion Criteria	• Individuals who underwent RT with or without chemotherapy, for tumors of the head and neck or chest for any malignant disorder, between 2008 and 2010, with information available on the studied variables
Exclusion Criteria	• None listed
Description of Study Protocol	• Intervention: 30 grams glutamine orally per day either early (before and during RT), or delayed (started after RT initiated), or no supplement given (control group) • Baseline anthropometry, gender distribution, and age did not differ between groups • Median dose of RT for head and neck group was 65 (60-70) Gy in 33 (30-35) sessions
Data Collection Summary	• OM and esophagitis assessed according to WHO criteria • Dependent Variables: incidence or severity of OM or esophagitis, nutrition status, number of RT treatment interruptions • Independent Variables: glutamine supplementation
Description of Actual Data Sample	• n= 117 (head and neck group = 79, consisting of 78 with HNC, 1 with melanoma on the head or neck; chest tumor group = 38, consisting of 29 with lung cancer, 6 with esophageal cancer and 3 with lymphoma) • Early Glutamine Group: 27.4% of participants • Delayed Glutamine Group: 49.5% of participants • No Glutamine Group: 23.1% of participants Location: Spain
Summary of Results	• Significantly less severe OM in the head and neck patients in the group that received “early” glutamine supplementation (p=0.039)

	• Those receiving glutamine (early or delayed) had a -9% reduced risk of developing OM (95% CI = -18% to -1%) • Significantly less weight loss during RT observed in head and neck patients in the group that received "early" glutamine compared to the other groups (p=0.009) • Significantly more head and neck patients in the no supplement group required tube feeding compared to the other two groups (p=0.04) • "Early" use of glutamine was associated with decreased risk of esophagitis. Significantly fewer chest tumor patients had weight loss of more than 5% in either treatment group compared to no supplement group (p = 0.027) • No significant differences found for interruptions in RT, hospitalizations, opioid analgesic use, or death during treatment • Only use of glutamine was related to incidence of OM after adjusting for sex, age, previous surgery, chemotherapy, and RT dose.
Author Conclusion	• The authors concluded that glutamine use was associated with significant reduction in the risk and severity of OM, weight loss, and tube feeding use. They also concluded that glutamine use was associated with significantly decreased risk of RT-induced esophagitis.
Reviewer Comments	• *Strengths of this study include that it examined two different intervention times for the glutamine supplementation. Additionally, it did examine nutritional status for each group, which can be a confounding factor to the development of OM.* • *Limitations include that all possible confounding factors not controlled for given the retrospective nature, only correlation could be determined and not causation, and convenience sampling was used which limits the applicability to the general population.*
Funding Source	• Not stated

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		

1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	No
2.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	No
2.2. Were criteria applied equally to all study groups?	2.2	Yes
2.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Unclear
3. Were <u>study groups comparable</u>?	3	Unclear
3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	No
3.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Unclear
3.3. Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	No
3.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A
4. Was method of handling <u>withdrawals</u> described?	4	N/A
4.1. Were follow up methods described and the same for all groups?	4.1	N/A
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	N/A
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4. Were reasons for withdrawals similar across groups	4.4	N/A
4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5. Was <u>blinding</u> used to prevent introduction of bias?	5	No
5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	N/A
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	N/A
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	No
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5. In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A

6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	6	No
6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	N/A
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Unclear
6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	No
6.6. Were extra or unplanned treatments described?	6.6	Yes
6.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Unclear
6.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were outcomes clearly defined and the measurements valid and reliable?	7	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
7.5. Was the measurement of effect at an appropriate level of precision?	7.5	Unclear
7.6. Were other factors accounted for (measured) that could affect outcomes?	7.6	No
7.7. Were the measurements conducted consistently across groups?	7.7	Yes
8. Was the statistical analysis appropriate for the study design and type of outcome indicators?	8	Yes
8.1. Were statistical analyses adequately describing the results reported appropriately?	8.1	Yes
8.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	N/A
8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	No
8.6. Was clinical significance as well as statistical significance reported?	8.6	Yes
8.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
9. **Are conclusions supported by results with biases and limitations taken into consideration?**	9	Yes
9.1. Is there a discussion of findings?	9.1	Yes
9.2. Are biases and study limitations identified and discussed?	9.2	Yes
10. Is bias due to study's funding or sponsorship unlikely?	10	Unclear
10.1. Were sources of funding and investigators' affiliations described?	10.1	No
10.2. Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅)		

If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*

Citation	AKMANSU, M., İREN, S., & GÜNTÜRKÜN, G. (2018). The Effect of Using Oral Glutamine on the Side Effect of Mucositis in Patients with Head and Neck Cancer Who Are Receiving Chemoradiotherapy: Retrospective Evaluation with Clinical and Immunological Parameters. Turkish Journal of Oncology / Türk Onkoloji Dergisi, 33(3), 115–121. https://doi.org/10.5505/tjo.2018.1803
Study Design	Retrospective Cohort Study
Class	B
Quality Rating	∅ (neutral)
Research Purpose	• Determine the relationships between glutamine supplementation and intensity and duration of OM, and on proinflammatory cytokines
Inclusion Criteria	• Patients with cancers of either the nasopharynx, larynx, oropharynx, or hypopharynx, who received RT with or without chemotherapy, between October 2008 and November 2009
Exclusion Criteria	• None stated
Description of Study Protocol	• Intervention: 10 grams powdered glutamine taken orally mixed with water or fruit juice every 8 hours, from the first to last day of RT • OM measured weekly during RT using Radiation Therapy Oncology Group (RTOG) scoring system • Changes in weight measured weekly • IL-1 beta, IL-6, and TNF-alpha were measured at baseline, during, and at conclusion of the study
Data Collection Summary	• Dependent Variables: intensity and duration of OM, proinflammatory cytokines • Independent Variables: glutamine supplementation
Description of Actual Data Sample	• N =28 • 18 received glutamine, 10 did not • Various chemotherapy regimens used, various amounts of RT received. No significant differences in gender, age, ECOG performance status, cancer stage or use of induction chemotherapy were found between the two groups. Location: Turkey
Summary of Results	• All 10 individuals in the non-intervention group experienced grade 2 or worse mucositis. 9 of the 18 individuals in the intervention group

	experienced grade 2 or worse mucositis. The other 9 experienced grade 1 or no mucositis • Significantly lower incidence of severe (grade 3 or worse) mucositis in the intervention group (p=0.008) • Significantly longer time to onset of OM in the intervention group (p=0.007) • OM occurred at a significantly higher median RT dose in the glutamine group (p=0.006) • No significant differences in serum pro-inflammatory levels
Author Conclusion	• The authors concluded that glutamine supplementation was well tolerated, has proven effects on OM, and should be investigated further for its possible effects on inflammation.
Reviewer Comments	• *A strength of this study was the consistent dosage of glutamine for all in the intervention group.* • *Limitations include small sample size from only one institution, retrospective design of the study, confounding factors could not be controlled for, convenience sampling was used which limits applicability to larger population, and only correlation could be determined, not causation.*
Funding Source	• Not stated

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3 Were the target population and setting specified?	1.3	Yes
2 Was the <u>selection</u> of study subjects/patients free from bias?	2	No
	2.1	No

	2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.2	Yes
	2.2 Were criteria applied equally to all study groups?	2.3	Yes
	2.3 Were health, demographics, and other characteristics of subjects described?	2.4	Unclear
	2.4 Were the subjects/patients a representative sample of the relevant population?		
3	**Were <u>study groups comparable</u>?**	3	Unclear
	3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Unclear
	3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Yes
	3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	No
	3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	No
	3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
	3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A
4	**Was method of handling <u>withdrawals</u> described?**	4	N/A
	4.1 Were follow up methods described and the same for all groups?	4.1	N/A
	4.2 Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	N/A
	4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
	4.4 Were reasons for withdrawals similar across groups	4.4	N/A
	4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5	**Was <u>blinding</u> used to prevent introduction of bias?**	5	No
	5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	N/A
	5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	N/A
	5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	No
	5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
	5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6	**Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?**	6	No
	6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	N/A
		6.2	N/A

6.2 In observational study, were interventions, study settings, and clinicians/provider described?	6.3	Yes
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.4	Unclear
6.4 Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.5	No
6.5 Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.6	Yes
6.6 Were extra or unplanned treatments described?	6.7	Unclear
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.8	N/A
6.8 In diagnostic study, were details of test administration and replication sufficient?		
7 Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
7.1 Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3 Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
7.5 Was the measurement of effect at an appropriate level of precision?	7.5	Unclear
7.6 Were other factors accounted for (measured) that could affect outcomes?	7.6	No
7.7 Were the measurements conducted consistently across groups?	7.7	Yes
8 Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1 Were statistical analyses adequately describing the results reported appropriately?	8.1	Yes
8.2 Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3 Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4 Was “intent to treat” analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	N/A
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	No
8.6 Was clinical significance as well as statistical significance reported?	8.6	Yes
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
9 **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Yes
9.1 Is there a discussion of findings?	9.1	Yes
9.2 Are biases and study limitations identified and discussed?	9.2	Yes
10 Is bias due to study’s <u>funding or sponsorship</u> unlikely?	10	Unclear
10.1 Were sources of funding and investigators’ affiliations described?	10.1	No
10.2 Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are “No,” the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		

NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.*
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*

Citation	Pachón Ibáñez, J., Pereira Cunill, J., Osorio Gómez, G., Irles Rocamora, J., Serrano Aguayo, P., Quintana Ángel, B., … García Luna, P. (2018). Prevention of oral mucositis secondary to antineoplastic treatments in head and neck cancer by supplementation with oral glutamine. Nutricion Hospitalaria, 35(2), 428–433. https://doi.org/10.20960/nh.1467
Study Design	Prospective Cohort Study
Class	B
Quality Rating	∅ (neutral)
Research Purpose	• Evaluate the relationship between incidence of OM and oral glutamine supplementation, with secondary objectives of determining incidence of odynophagia, cancer treatment interruptions, need for analgesia and nasogastric tubes
Inclusion Criteria	• Stage I-IV cancers of the oral cavity, oropharynx, supraglottis, glottis, nasopharynx, hypopharynx, or paranasal sinuses, undergoing curative RT of 70 Gy by 2 Gy/day, with or without chemotherapy, surgery, or a monoclonal antibody drug • No specified length of RT treatment needed to be included in study, no drop outs noted • No mucositis at baseline • No other prophylactic measures
Exclusion Criteria	• None stated
Description of Study Protocol	• Intervention: 10 grams of glutamine taken every 8 hours throughout RT, versus no intervention in control group • Mucositis and odynophagia were rated once per week using RTOG/EORTC scales • Supportive treatment was prescribed as necessary (frequency or type of prescriptions not specified)
Data Collection Summary	• Dependent Variables: incidence of OM, odynophagia, cancer treatment interruptions, need for analgesia, and nasogastric tubes • Independent Variables: glutamine supplementation

Description of Actual Data Sample	• n=262, 131 in intervention group and 131 in control group • No differences in locations of or stages of malignancies between groups, or in types of treatment received++ Location: Spain
Summary of Results	• Control group had RR of developing mucositis of 1.78 in comparison to intervention group (p=0.047) • Significantly decreased need for nasogastric tube feeding in intervention group (p= 0.02), cancer treatment discontinuation (p=0.002), and prescriptions for analgesia (p=0.03) • Malignancies of oral cavity were associated with a significantly higher incidence of mucositis in comparison to the other included cancers • Odynophagia present in significantly more individuals in control group (p=0.0001), control group also experienced significantly higher incidence of severe odynophagia (p<0.0001) • Age, sex, body mass index at baseline, smoking, alcohol drinking habits, cancer stages and chemotherapy we all not associate with presence of mucositis when multivariate analysis was performed.
Author Conclusion	• Researchers concluded that oral glutamine significantly decreased incidence of OM, as well as incidence and severity of odynophagia.
Reviewer Comments	• Strengths of this study included the large sample size, prospective nature and similarity between intervention and control groups. • *Limitations include that it was not stated how compliance was verified, the length of intervention not specified, and no randomization or blinding was done. Additionally, potential confounding factors such as nutrition status throughout treatment, antibiotic use, and oral hygiene practices were not controlled for. Participants may have also received glutamine in enteral nutrition during the study period whether or not they were in the intervention group.*
Funding Source	• Not stated

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes

If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the research question clearly stated?	1	Yes
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.1 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.2 Were the target population and setting specified?	1.3	Yes
2 Was the selection of study subjects/patients free from bias?	2	Unclear
2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2 Were criteria applied equally to all study groups?	2.2	Yes
2.3 Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4 Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
3 Were study groups comparable?	3	Unclear
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	No
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Yes
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	No
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A
4 Was method of handling withdrawals described?	4	No
4.1 Were follow up methods described and the same for all groups?	4.1	Yes
4.2 Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	No
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4 Were reasons for withdrawals similar across groups	4.4	Unclear
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5 Was blinding used to prevent introduction of bias?	5	No
5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	No

	5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	No
	5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
	5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?**	6	No
	6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
	6.2 In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
	6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
	6.4 Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Unclear
	6.5 Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	No
	6.6 Were extra or unplanned treatments described?	6.6	No
	6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Unclear
	6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7	**Were outcomes clearly defined and the measurements valid and reliable?**	7	Yes
	7.1 Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
	7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
	7.3 Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
	7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
	7.5 Was the measurement of effect at an appropriate level of precision?	7.5	Yes
	7.6 Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
	7.7 Were the measurements conducted consistently across groups?	7.7	Yes
8	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	8	Yes
	8.1 Were statistical analyses adequately describing the results reported appropriately?	8.1	Yes
	8.2 Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
	8.3 Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
	8.4 Was “intent to treat” analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	No
	8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
	8.6 Was clinical significance as well as statistical significance reported?	8.6	Yes
	8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A

9 **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?** 9.1 Is there a discussion of findings? 9.2 Are biases and study limitations identified and discussed?	9 9.1 9.2	Yes Yes Yes
10 Is bias due to study's <u>funding or sponsorship</u> unlikely? 10.1Were sources of funding and investigators' affiliations described? 10.2Was there no apparent conflict of interest?	10 10.1 10.2	Unclear No Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

Citation	Huang, E., Leung, S., Wang, C., Chen, H., Sun, L., Fang, F., … Hsiung, C. (2000). Oral glutamine to alleviate radiation-induced oral mucositis: a pilot randomized trial. International Journal of Radiation Oncology, Biology, Physics, 46(3), 535–539. https://doi.org/10.1016/S0360-3016(99)00402-2
Study Design	Single-Blinded, Randomized Controlled Trial
Class	A
Quality Rating	+ (positive)
Research Purpose	• Evaluated the effect of oral glutamine supplementation on OM
Inclusion Criteria	• HNC of the nasopharynx, oropharynx, or oral cavity, undergoing RT • Tolerate solid food at baseline • At least ½ of the oral cavity needed to be included in RT field
Exclusion Criteria	• Presence of mouth sores at baseline, diabetes, trismus, received chemotherapy in addition to RT, used other prophylactic drugs or mouthwashes, or had a Karnofsky's Performance Status < 70
Description of Study Protocol	• Intervention: Swish and spit out 2 grams of glutamine powder in 30 ml normal saline, four times per day, throughout RT • RT schedule was 1.8 Gy/fraction, in 25 fractions (5 weeks) • Objective mucositis graded each treatment day using RTOG/EORTC criteria • Weight checked once per week • Medication was prescribed when patients became symptomatic
Data Collection Summary	• Dependent Variables: oral mucositis • Independent Variables: glutamine supplementation

Description of Actual Data Sample	• n= 17 (8 in intervention group and 9 in control) • No significant differences in smoking, alcohol use, betel nut chewing, age, gender, body weight, body weight change, or diagnosis between the two groups Location: Taiwan
Summary of Results	• Significantly less severe objective OM in glutamine group (p=0.006) • Significantly shorter time of duration of subjective grade 3 or higher (severe OM) in the glutamine group (p=0.0386) • No difference between analgesic drug use, mean body weight change
Author Conclusion	• Researchers concluded that severity and duration of objective OM may be significantly reduced by oral glutamine supplementation, and that glutamine may specifically shorten the duration of grade 3 or worse subjective OM.
Reviewer Comments	• *Strengths of this study include its placebo controlled, RCT design, and that it controlled for weight change during the trial, betel nut, tobacco, and alcohol use, and use of prophylactic drugs or other mouthwashes. Additionally, all patients received the same RT treatment during the study, and chemotherapy was not used.* • *Limitations include that the sample size was very small, was completed at only one institution, and was only single-blinded. Additionally, oral hygiene practices were not controlled for.*
Funding Source	• Not stated

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.1 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.2 Were the target population and setting specified?	1.3	Yes

2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2 Were criteria applied equally to all study groups?	2.2	Yes
2.3 Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4 Were the subjects/patients a representative sample of the relevant population?	2.4	Unclear
3 Were <u>study groups comparable</u>?	3	Yes
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Yes
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Yes
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A
4 Was method of handling <u>withdrawals</u> described?	4	No
4.1 Were follow up methods described and the same for all groups?	4.1	Yes
4.2 Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	No
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4 Were reasons for withdrawals similar across groups	4.4	Unclear
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5 Was <u>blinding</u> used to prevent introduction of bias?	5	Yes
5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	No
5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	No
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6 Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
6.2 In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A

6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
6.4 Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Unclear
6.5 Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	Yes
6.6 Were extra or unplanned treatments described?	6.6	Yes
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Unclear
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7 Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
7.1 Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3 Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
7.5 Was the measurement of effect at an appropriate level of precision?	7.5	Yes
7.6 Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
7.7 Were the measurements conducted consistently across groups?	7.7	Yes
8 Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1 Were statistical analyses adequately describing the results reported appropriately?	8.1	Yes
8.2 Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3 Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	N/A
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
8.6 Was clinical significance as well as statistical significance reported?	8.6	Yes
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
9 **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Yes
9.1 Is there a discussion of findings?	9.1	Yes
9.2 Are biases and study limitations identified and discussed?	9.2	Yes
10 Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Unclear
10.1 Were sources of funding and investigators' affiliations described?	10.1	No
10.2 Was there no apparent conflict of interest?	10.2	Yes

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.

NEUTRAL (∅)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.

PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Citation	Chattopadhyay, S., Saha, A., Azam, M., Mukherjee, A., & Sur, P. (2014). Role of oral glutamine in alleviation and prevention of radiation-induced oral mucositis: A prospective randomized study. South Asian Journal of Cancer, 3(1), 8–12. https://doi.org/10.4103/2278-330X.126501
Study Design	Randomized Controlled Trial
Class	A
Quality Rating	∅ (Neutral)
Research Purpose	• Compare the effect of oral glutamine supplementation on OM
Inclusion Criteria	• Stage I-IV HNC of the oral cavity, larynx, hypopharynx, nasopharynx, or oropharynx, undergoing RT with or without chemotherapy • Performance status not worse than 50% on Karnofsky performance status scale
Exclusion Criteria	• Prior RT, RT not intended to be curative
Description of Study Protocol	• Intervention: 10 grams of glutamine powder suspended in 1000 ml of water, swished and swallowed daily on cancer treatment days 2 hours before treatment • Patients who were able to take on average at least 800 ml daily were included • RT given at 2 Gy/fraction, 5 days per week, until grade 3 or 4 OM developed • Patients stratified according to age (<60 or >60 years), RT treatment field • OM was assessed weekly using the WHO method
Data Collection Summary	• Dependent Variables: oral mucositis • Independent Variables: glutamine supplementation
Description of Actual Data Sample	• n= 70 (35 in intervention group and 35 in control), no dropouts recorded • No significant difference between groups in age, sex, tumor location, stage of disease, treatment provided, and RT treatment sites Location: India
Summary of Results	• Intervention group had significantly less frequent grade 3 (p=0.02) and grade 4 OM (p=0.04) • Intervention group had significantly longer time to onset of OM (p<0.001) and significantly shorter duration of severe (grade III or worse) OM (p<0.001) • When analyzed by cancer treatment, those in intervention group only receiving RT and not chemotherapy did not experience a statistically

	significant difference in incidence of OM compared to control group. Those in the intervention group receiving chemotherapy had significantly less severe OM than the control group participants receiving chemotherapy.
Author Conclusion	• Researchers concluded that glutamine showed improvements in OM appearance, incidence, duration and severity.
Reviewer Comments	• *A strength of this study is its design as a RCT, as well as the similarities in groups in several areas including age, sex, tumor location, stage of disease, treatment provided, and RT treatment sites.* • *Limitations of this study were the lack of blinding, the fairly small sample size, and that potential confounding factors such as suboptimal oral hygiene, lower than average nutritional status, no antibiotic use early in OM, and alcohol and tobacco use were not evaluated between groups. Additionally, this was a single institution study, thus limiting applicability of results to the broader population.*
Funding Source	• Glutamine packets were provided free of cost by GLS Pharmaceuticals; this was approved by the institutional ethical committee.

Relevance Questions		
5. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
6. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
7. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
8. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3 Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
	2.2	Yes

2.2 Were criteria applied equally to all study groups? 2.3 Were health, demographics, and other characteristics of subjects described? 2.4 Were the subjects/patients a representative sample of the relevant population?	2.3 2.4	Yes Unclear
3. Were <u>study groups comparable</u>? 3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) 3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? 3.3 Were concurrent controls used? (Concurrent preferred over historical controls.) 3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? 3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) 3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3 3.1 3.2 3.3 3.4 3.5 3.6	Yes Yes Yes Yes Yes N/A N/A
4. Was method of handling <u>withdrawals</u> described? **4.1** Were follow up methods described and the same for all groups? 4.2 Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.) 4.3 Were all enrolled subjects/patients (in the original sample) accounted for? 4.4 Were reasons for withdrawals similar across groups 4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4 4.1 4.2 4.3 4.4 4.5	Yes Yes Yes Yes N/A N/A
5. Was <u>blinding</u> used to prevent introduction of bias? **5.1** In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate? 5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) 5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? 5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status? 5.5 In diagnostic study, were test results blinded to patient history and other test results?	5 5.1 5.2 5.3 5.4 5.5	No No No No N/A N/A
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described? 6.1 In RCT or other intervention trial, were protocols described for all regimens studied? 6.2 In observational study, were interventions, study settings, and clinicians/provider described?	6 6.1 6.2 6.3 6.4	Unclear Yes N/A Yes Yes

6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? 6.4 Was the amount of exposure and, if relevant, subject/patient compliance measured? 6.5 Were co-interventions (e.g., ancillary treatments, other therapies) described? 6.6 Were extra or unplanned treatments described? 6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? 6.8 In diagnostic study, were details of test administration and replication sufficient?	6.5 6.6 6.7 6.8	No No Unclear N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>? 7.1 Were primary and secondary endpoints described and relevant to the question? 7.2 Were nutrition measures appropriate to question and outcomes of concern? 7.3 Was the period of follow-up long enough for important outcome(s) to occur? 7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? 7.5 Was the measurement of effect at an appropriate level of precision? 7.6 Were other factors accounted for (measured) that could affect outcomes? 7.7 Were the measurements conducted consistently across groups?	7 7.1 7.2 7.3 7.4 7.5 7.6 7.7	Yes Yes No Yes Yes Yes No Yes
8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators? 8.1 Were statistical analyses adequately describing the results reported appropriately? 8.2 Were correct statistical tests used and assumptions of test not violated? 8.3 Were statistics reported with levels of significance and/or confidence intervals? 8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? 8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? 8.6 Was clinical significance as well as statistical significance reported? 8.7 If negative findings, was a power calculation reported to address type 2 error?	8 8.1 8.2 8.3 8.4 8.5 8.6 8.7	Yes Yes Yes Yes N/A No Yes N/A
9. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?** 9.1 Is there a discussion of findings? 9.2 Are biases and study limitations identified and discussed?	9 9.1 9.2	Yes Yes Yes
10. Is bias due to study's <u>funding or sponsorship</u> unlikely? 10.1 Were sources of funding and investigators' affiliations described? 10.2 Was there no apparent conflict of interest?	10 10.1 10.2	Unclear Yes Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅)		

If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*

Citation	Pathak, S., Soni, T., Sharma, L., Patni, N., & Gupta, A. (2019). A Randomized Controlled Trial to Evaluate the Role and Efficacy of Oral Glutamine in the Treatment of Chemo-radiotherapy-induced Oral Mucositis and Dysphagia in Patients with Oropharynx and Larynx Carcinoma. Cureus, 11(6), e4855. https://doi.org/10.7759/cureus.4855
Study Design	Randomized Controlled Trial
Class	A
Quality Rating	∅ (neutral)
Research Purpose	• Examine if oral glutamine supplementation decreases incidence or severity of OM or dysphagia • Secondary objectives included time to onset of OM and dysphagia, incidence of treatment interruptions, and significant weight reductions
Inclusion Criteria	• Stage III-IV oropharynx or larynx cancer, undergoing concurrent chemoradiation • > 18 to < 70 years old
Exclusion Criteria	• None stated
Description of Study Protocol	• Intervention: 10 grams of glutamine taken orally once per day on treatment days, throughout 7-week cancer treatment • All received 70 Gy RT in 35 fractions and weekly cisplatin dosed based on body surface area • Grading of mucositis and dysphagia was completed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 • Mucositis, dysphagia, weight loss, and cancer treatment compliance were measured weekly until the end of treatment
Data Collection Summary	• Dependent Variables: oral mucositis, dysphagia • Independent Variables: glutamine supplementation
Description of Actual Data Sample	• Initial enrollment: n=60 (30 in each group) • Attrition: n= 56 (completed full treatment), 1 patient from each group died due to myocardial infarction, and 1 patient from each group did not complete the full treatment • Age, sex, and cancer type were similar between groups

	Location: India
Summary of Results	• All experienced grade II OM or worse by the seventh week • Significantly less severe OM in intervention group at the seventh week of treatment ($p<0.001$) • Significantly longer time to onset of OM • Intervention group had less severe dysphagia and a longer time to onset of dysphagia • Intervention group had significantly less participants who experienced weight loss ($p=0.004$), significantly less treatment interruptions ($p=0.025$), need for nasogastric tube feeding ($p=0.03$), and incidence of severe toxicity ($p=0.03$)
Author Conclusion	• Researchers concluded that incidence and severity of chemoradiotherapy-induced OM and dysphagia were reduced with the use of glutamine.
Reviewer Comments	• *Strengths of this study include that it was a randomized controlled trial and that the patients received the exact same cancer treatment in both groups. The study also had an adequate number of participants complete the protocol to allow for the researcher's goal of eighty percent study power (23 participants in each study arm).* • *Limitations include that the study was not blinded, did not have a placebo, and still had a rather small sample size located in only one geographical area (at one hospital). Finally, the study did not assess for possible confounding factors such as BMI, nutrition status of patients at baseline (other than patients being "appropriate for treatment"), tobacco use, oral hygiene care adequacy, or use of antibiotics for OM.*
Funding Source	• No financial support received from any organization

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		

1. Was the <u>research question</u> clearly stated?	1	Yes
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3 Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2 Were criteria applied equally to all study groups?	2.2	Yes
2.3 Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4 Were the subjects/patients a representative sample of the relevant population?	2.4	Unclear
3. Were <u>study groups comparable</u>?	3	Unclear
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Yes
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	No
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A
4. Was method of handling <u>withdrawals</u> described?	4	Yes
4.1 Were follow up methods described and the same for all groups?	4.1	Yes
4.2 Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4 Were reasons for withdrawals similar across groups	4.4	Yes
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5. Was <u>blinding</u> used to prevent introduction of bias?	5	No
5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	No
5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	No
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A

5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	6	No
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
6.2 In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
6.4 Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Unclear
6.5 Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	No
6.6 Were extra or unplanned treatments described?	6.6	No
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Unclear
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were outcomes clearly defined and the measurements valid and reliable?	7	Yes
7.1 Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	No
7.3 Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
7.5 Was the measurement of effect at an appropriate level of precision?	7.5	Yes
7.6 Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
7.7 Were the measurements conducted consistently across groups?	7.7	Yes
8. Was the statistical analysis appropriate for the study design and type of outcome indicators?	8	Yes
8.1 Were statistical analyses adequately describing the results reported appropriately?	8.1	Yes
8.2 Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3 Were statistics reported with levels of significance and/or confidence intervals?	8.3	Unclear
8.4 Was “intent to treat” analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	No
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
8.6 Was clinical significance as well as statistical significance reported?	8.6	N/A
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7	
9. **Are conclusions supported by results with biases and limitations taken into consideration?**	9	Yes
9.1 Is there a discussion of findings?	9.1	Yes
9.2 Are biases and study limitations identified and discussed?	9.2	Yes

10. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
10.1Were sources of funding and investigators' affiliations described?	10.1	Yes
10.2Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

Citation	Pattanayak, L., Panda, N., Dash, M. K., Mohanty, S., & Samantaray, S. (2016). Management of Chemoradiation-Induced Mucositis in Head and Neck Cancers With Oral Glutamine. Journal of Global Oncology, 2(4), 200–206. https://doi.org/10.1200/JGO.2015.000786
Study Design	Randomized Controlled Trial
Class	A
Quality Rating	∅ (neutral)
Research Purpose	• Examine the efficacy and safety of oral glutamine supplementation on HNC patients undergoing chemoradiation
Inclusion Criteria	• HNC patients with stage II-IV cancer of the oral cavity, oropharynx, hypopharynx, larynx, or nasopharynx, who underwent chemoradiation • Age 20-80 years old • No distant metastases • Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 • Normal hematologic and biochemical parameters
Exclusion Criteria	• Previous surgery in the head and neck, previous chemotherapy or RT, uncontrolled widely spread disease, diagnosis of a synchronous double primary malignancy, or participation in another clinical trial
Description of Study Protocol	• Intervention: Swish and swallow 15 grams of glutamine suspended in a glass of water twice per day throughout treatment • All received 70 Gy RT in 35 fractions over 7 weeks with weekly concurrent cisplatin • Patients examined once per week for presence and severity of mucositis, pain, use of analgesics, and nasogastric feeding tube

Data Collection Summary	• Dependent Variables: oral mucositis • Independent Variables: glutamine supplementation
Description of Actual Data Sample	• n= 162 (81 in intervention and 81 in control) • No dropouts, but some had treatment delays due to mucositis, and not all completed the weekly cisplatin for all seven weeks • Age, sex, addictions to smoking and chewing tobacco, diagnosis, treatment sites and differentiation, and tumor stage were not significantly different between groups. Location: India
Summary of Results	• Significantly decreased severity of OM in intervention group ($p<0.05$) • Significantly delayed time to onset of OM ($p<0.05$) • Adverse events such as pain, dysphagia, nausea, edema, and cough were significantly more common in the control group than in the intervention group
Author Conclusion	• Researchers concluded that mucositis was less severe and had a longer time to onset when glutamine was used.
Reviewer Comments	• *Strengths of this study include its RCT design, fairly large sample size, inclusion of tobacco and betel nut use when comparing the control and intervention groups, and standardized cancer treatments between the two groups.* • *Limitations include that the study was not blinded and did not assess for other possible confounding factors such as suboptimal oral hygiene, lower than average nutritional status, or no antibiotic or other prophylactic use early in OM.*
Funding Source	• Not stated

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
	1.1	Yes

1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.2	Yes
1.2Was the outcome(s) (dependent variable(s)) clearly indicated?	1.3	Yes
1.3 Were the target population and setting specified?		
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.1 Were criteria applied equally to all study groups?	2.2	Yes
2.2 Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.3 Were the subjects/patients a representative sample of the relevant population?	2.4	Unclear
3 Were <u>study groups comparable</u>?	3	Unclear
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Yes
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Unclear
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A
4 Was method of handling <u>withdrawals</u> described?	4	Yes/ N/A
4.1 Were follow up methods described and the same for all groups?	4.1	Yes
4.2 Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	No
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4 Were reasons for withdrawals similar across groups	4.4	N/A
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5 Was <u>blinding</u> used to prevent introduction of bias?	5	No
5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	No
5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	No
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A

6	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?**	6	Yes
	6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
	6.2 In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
	6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
	6.4 Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	No
	6.5 Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	Yes
	6.6 Were extra or unplanned treatments described?	6.6	Yes
	6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Unclear
	6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7	**Were outcomes clearly defined and the measurements valid and reliable?**	7	Yes
	7.1 Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
	7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
	7.3 Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
	7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
	7.5 Was the measurement of effect at an appropriate level of precision?	7.5	Yes
	7.6 Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
	7.7 Were the measurements conducted consistently across groups?	7.7	Yes
8	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	8	Yes
	8.1 Were statistical analyses adequately describing the results reported appropriately?	8.1	Yes
	8.2 Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
	8.3 Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
	8.4 Was “intent to treat” analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	No
	8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	No
	8.6 Was clinical significance as well as statistical significance reported?	8.6	Yes
	8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
9	**Are conclusions supported by results with biases and limitations taken into consideration?**	9	Yes
	9.1 Is there a discussion of findings?	9.1	Yes
	9.2 Are biases and study limitations identified and discussed?	9.2	Yes
10	**Is bias due to study’s funding or sponsorship unlikely?**	10	Unclear
	10.1 Were sources of funding and investigators’ affiliations described?	10.1	No

10.2Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

Citation	Tsujimoto, T., Yamamoto, Y., Wasa, M., Takenaka, Y., Nakahara, S., Takagi, T., … Ito, T. (2015). 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. Oncology Reports, 33(1), 33–39. https://doi.org/10.3892/or.2014.3564
Study Design	Double Blind, Placebo-Controlled Randomized Controlled Trial
Class	A
Quality Rating	+ (positive)
Research Purpose	• To evaluate if glutamine decreases the severity of OM, as well as mucositis of the pharynx and larynx • Secondary objectives were to determine duration and time to onset of mucositis, pain, incidence and duration of opioid use, total opioid use, need for and duration of nutritional supplementation via feeding tube or peripheral parenteral nutrition, and clinical data
Inclusion Criteria	• HNC patients with stage II-IV cancers of the nasopharynx, oropharynx, hypopharynx, or larynx, undergoing chemoradiation for 6 weeks (uniform treatment for all patients)
Exclusion Criteria	• Active mouth or throat soreness before treatment, uncontrolled diabetes mellitus, or severe real or hepatic insufficiency
Description of Study Protocol	• Intervention: 10 grams of glutamine, taken orally three times per day throughout cancer treatment, or 10 grams of placebo three times per day • Mucositis assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0
Data Collection Summary	• Dependent Variables: oral mucositis, mucositis of pharynx or larynx • Independent Variables: glutamine supplementation
Description of Actual Data Sample	• Initial enrollment: n=50 • Final assessment: n= 40 (20 in intervention, 20 in placebo group)

	• No significant differences between groups in sex, age, primary tumor location or stage, ECOG performance status, total dose of RT, total doses of chemotherapy, diabetes mellitus, biochemical parameters including serum proteins, weight loss, body mass index change, or daily intake of calories Location: Japan
Summary of Results	• Significantly decreased mean maximal mucositis grade in the intervention group (p=0.005) • No significant differences in time to onset of mucositis, duration, or mean time to onset of severe mucositis • Average mucositis grade was significantly higher in the placebo group at weeks 5 and 6 • Pain scores were significantly lower in the intervention group during weeks 4, 5 and 6 • Average length of time opioids were used was significantly longer in placebo group • Average length of time nutrition supplementation needed was significantly longer in placebo group
Author Conclusion	• Researchers concluded that mucositis severity was significantly decreased with the use of glutamine.
Reviewer Comments	• *This trial had significant strengths, including the design as a double-blinded, placebo-controlled RCT. Additionally, the intervention and control groups were very comparable, including standardized cancer treatment and no differences in BMI change, weight change and daily caloric intake between groups. The groups also had supervised oral hygiene care and assessment throughout the study by a nurse which is important as oral hygiene care adequacy is a known risk factor for mucositis.* • *Limitations of this study include that groups were not controlled for tobacco use. Additionally, though oral hygiene was supervised throughout the treatment, the researchers did not specify if other prophylactic rinses or supplements were used by the participants. The sample size of this study was also fairly small.*
Funding Source	• Emmaus Medical, Inc. provided glutamine supplements and Matsutani Chemical Industry Co., Inc. provided placebo

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes

2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3Were the target population and setting specified?	1.3	Yes
2 Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2 Were criteria applied equally to all study groups?	2.2	Yes
2.3 Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4 Were the subjects/patients a representative sample of the relevant population?	2.4	Unclear
3 Were <u>study groups comparable</u>?	3	Yes
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Yes
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Unclear
3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A
4 Was method of handling <u>withdrawals</u> described?	4	Yes
4.1 Were follow up methods described and the same for all groups?	4.1	Yes
4.2 Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4 Were reasons for withdrawals similar across groups	4.4	Yes
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5 Was <u>blinding</u> used to prevent introduction of bias?	5	Yes

5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	Yes
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	Yes
5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	Unclear
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6 Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
6.2 In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
6.4 Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Yes
6.5 Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	Yes
6.6 Were extra or unplanned treatments described?	6.6	Yes
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Yes
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7 Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
7.1 Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3 Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
7.5 Was the measurement of effect at an appropriate level of precision?	7.5	Yes
7.6 Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
7.7 Were the measurements conducted consistently across groups?	7.7	Yes
8 Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1 Were statistical analyses adequately describing the results reported appropriately?	8.1	Yes
8.2 Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3 Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4 Was “intent to treat” analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	Unclear
	8.5	Yes

8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? 8.6 Was clinical significance as well as statistical significance reported? 8.7 If negative findings, was a power calculation reported to address type 2 error?	8.6	Unclear
	8.7	N/A
9 **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	No
9.1 Is there a discussion of findings?	9.1	Yes
9.2 Are biases and study limitations identified and discussed?	9.2	No
10 Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Unclear
10.1Were sources of funding and investigators' affiliations described?	10.1	No
10.2Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

Citation	Huang, C., Huang, M., Fang, P., Chen, F., Wang, Y., Chen, C., … Lee, H. (2019). Randomized double-blind, placebo-controlled trial evaluating oral glutamine on radiation-induced oral mucositis and dermatitis in head and neck cancer patients. The American Journal of Clinical Nutrition, 109(3), 606–614. https://doi.org/10.1093/ajcn/nqy329
Study Design	Double blinded, placebo controlled, randomized controlled trial
Class	A
Quality Rating	∅
Research Purpose	• Examine whether oral glutamine decreased OM and neck dermatitis while patients underwent intensity-modulated RT with or without chemotherapy
Inclusion Criteria	• HNC patients with stage I-IV HNC, most with oral cavity cancer (65.6%), but also could have nasopharynx, oropharynx, hypopharynx, or larynx cancers • Must have had healthy oral mucosa at baseline
Exclusion Criteria	• Diabetes mellitus, renal or hepatic insufficiency, history of prior RT or sepsis, distant metastasis, or Eastern Cooperative Oncology Group (ECOG) performance status score greater than or equal to 2

Description of Study Protocol	• Intervention: 10 grams of glutamine dissolved in cold water three times per day before a meal starting 1 week before RT and ending 2 weeks after RT completion, versus placebo of maltodextrin • Dermatitis and mucositis assessed weekly according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3
Data Collection Summary	• Dependent Variables: oral mucositis, neck dermatitis • Independent Variables: glutamine supplementation
Description of Actual Data Sample	• Initial enrollment: n=71 • Final population who completed RT: n= 64 (intervention group = 31, placebo = 33) • Most (65.6%) of participants had oral cavity cancer • No significant differences between groups in age, sex, primary tumor location or stage, ECOG performance status, precious operations, total dose of RT, maximum or mean RT dose to oral cavity, use of chemotherapy (yes or no), hypertension, alcohol use, betel use, cigarette use, BMI, recommended or estimated daily calorie intake, opioid use or number of RT interruption days Location: Taiwan
Summary of Results	• Decreased mean maximum severity of mucositis in intervention group, however not significant • No significant difference in incidence or severity of dermatitis • Strong correlation found between decrease in BMI and severity of OM
Author Conclusion	• Researchers concluded that there was a strong correlation between decrease in BMI and OM, but not between glutamine use and OM, or between glutamine use and neck dermatitis.
Reviewer Comments	• *Strengths of this study include RCT design with doubling blinding and placebo control, assessment and similarity between groups of tobacco, alcohol and betel nut use, BMI, prognostic nutritional index, and daily caloric intake. Also, participants were not allowed to use any other nutritional supplements during the trial.* • *this study include the fairly small sample size, the variety of chemotherapy agents as well as chemotherapy administration frequencies patients received, and the drop out of patients in the placebo arm due to aversion of the placebo product, and the lack of assessment of antibiotic use, or oral hygiene care adequacy between groups. Also, there was no way to prove the protocol was followed by all patients, since the doses were self-administered. Further, seven patients did not complete RT, which the authors acknowledged could have affected randomization. The researchers also noted that their study may have been underpowered, and that the high number of patients with oral cavity cancer may have contributed to the results,*

	as this type of cancer involves more severe RT to the oral cavity, thus making it possible that worse OM could develop compared to the other cancer types. • *Though results were not significant they were positive.*
Funding Source	• Grants provided by Kaohsiung Medical University. Researchers indicated that this had no impact on study design, data collection or analysis, or decision to publish.

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.1 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.2 Were the target population and setting specified?	1.3	Yes
2 Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2 Were criteria applied equally to all study groups?	2.2	Yes
2.3 Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4 Were the subjects/patients a representative sample of the relevant population?	2.4	Unclear
3 Were <u>study groups comparable</u>?	3	Yes
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Yes
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Unclear

3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A
4 Was method of handling withdrawals described?	4	Yes
4.1 Were follow up methods described and the same for all groups?	4.1	Yes
4.2 Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	No
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4 Were reasons for withdrawals similar across groups	4.4	Unclear
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5 Was blinding used to prevent introduction of bias?	5	Yes
5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	Yes
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	Yes
5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	Yes
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6 Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	6	Unclear
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
6.2 In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
6.4 Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Unclear
6.5 Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	No
6.6 Were extra or unplanned treatments described?	6.6	Yes
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Unclear
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7 Were outcomes clearly defined and the measurements valid and reliable?	7	Yes
7.1 Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
	7.3	Yes
	7.4	Yes

7.3 Was the period of follow-up long enough for important outcome(s) to occur?	7.5	Yes
7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.6	Yes
7.5 Was the measurement of effect at an appropriate level of precision? 7.6 Were other factors accounted for (measured) that could affect outcomes? 7.7 Were the measurements conducted consistently across groups?	7.7	Yes
8 Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1 Were statistical analyses adequately describing the results reported appropriately?	8.1	Yes
8.2 Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3 Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	N/A
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
8.6 Was clinical significance as well as statistical significance reported?	8.6	Yes
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7	Yes
9 **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Yes
9.1 Is there a discussion of findings?	9.1	Yes
9.2 Are biases and study limitations identified and discussed?	9.2	Yes
10 Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
10.1 Were sources of funding and investigators' affiliations described?	10.1	Yes
10.2 Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

Citation	Lopez-Vaquero, D., Gutierrez-Bayard, L., Rodriguez-Ruiz, J.-A., Saldaña-Valderas, M., & Infante-Cossio, P. (2017). Double-blind randomized study of oral glutamine on the management of radio/chemotherapy-induced mucositis and dermatitis in head and neck cancer. Molecular and Clinical Oncology, 6(6), 931–936. https://doi.org/10.3892/mco.2017.1238
Study Design	Randomized Controlled Trial

Class	A
Quality Rating	+ (positive)
Research Purpose	• Examine if glutamine supplementation would reduce incidence or severity of OM and dermatitis
Inclusion Criteria	• HNC patients with cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx, underwent RT with or without chemotherapy for 6 weeks • Performance status of 0 or 1 according to ECOG
Exclusion Criteria	• History of previous RT, uncontrolled systemic disease, presence of synchronous double malignant tumor, hypersensitivity or allergy to any of the components in the study, uncontrolled diabetes mellitus, severe kidney or liver failure, skin diseases or autoimmune diseases
Description of Study Protocol	• Intervention: Ten grams of glutamine dissolved in water three times per day with meals or placebo (maltodextrin) • Mucositis was assessed according to the Common Terminology Criteria for Adverse Events
Data Collection Summary	• Dependent Variables: oral mucositis, dermatitis • Independent Variables: glutamine supplementation
Description of Actual Data Sample	• Initial enrollment: n=50 • Final attrition: n= 49 (24 in control group and 25 in intervention group) • No difference between groups in sex, age, tobacco use, alcohol use, median weight, median pain, primary tumor site or histopathology, or performance status. Location: Spain
Summary of Results	• No significant difference in incidence of OM, although placebo group had higher values • No significant difference in severity of OM, although the placebo group had higher values • Intervention group had significantly less incidence and severity of neck dermatitis • No significant difference in weight loss between groups
Author Conclusion	• Researchers concluded that slight clinical effects were seen with the use of oral glutamine, although results were not significant. Results did suggest a significant reduction in incidence and severity of dermatitis.
Reviewer Comments	• *Strengths of this study include its gold standard design as a double-blind, placebo-controlled RCT. Also, the study controlled for weight change, alcohol and tobacco use in participant groups, and cancer treatment. Additionally, intervention compliance measurement (100%) was completed.*

	• *Limitations of this study include that it was completed at only one institution and had a fairly small sample size. Also, oral hygiene adequacy during treatment was not measured. Though this study did not find significant positive results for glutamine's impact on OM, the results did trend towards significance.*
Funding Source	• L-glutamine supplement was provided by Nutrition Medica S.L. Laboratories.

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.1 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.2 Were the target population and setting specified?	1.3	Yes
2 Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2 Were criteria applied equally to all study groups?	2.2	Yes
2.3 Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4 Were the subjects/patients a representative sample of the relevant population?	2.4	Unclear
3 Were <u>study groups comparable</u>?	3	Yes
3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Yes
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Yes

3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A
4 Was method of handling withdrawals described?	4	Yes
4.1 Were follow up methods described and the same for all groups?	4.1	Yes
4.2 Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4 Were reasons for withdrawals similar across groups	4.4	Yes
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5 Was blinding used to prevent introduction of bias?	5	Yes
5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	Yes
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	Yes
5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	Yes
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6 Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	6	Yes
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
6.2 In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
6.4 Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Yes
6.5 Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	Yes
6.6 Were extra or unplanned treatments described?	6.6	Yes
6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Yes
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7 Were outcomes clearly defined and the measurements valid and reliable?	7	Yes
7.1 Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
	7.3	Yes
	7.4	Yes

7.3 Was the period of follow-up long enough for important outcome(s) to occur?	7.5	Yes
7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.6	Yes
7.5 Was the measurement of effect at an appropriate level of precision? 7.6 Were other factors accounted for (measured) that could affect outcomes? 7.7 Were the measurements conducted consistently across groups?	7.7	Yes
8 Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1 Were statistical analyses adequately describing the results reported appropriately?	8.1	Yes
8.2 Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3 Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	N/A
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
8.6 Was clinical significance as well as statistical significance reported?	8.6	Yes
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
9 **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Yes
9.1 Is there a discussion of findings?	9.1	Yes
9.2 Are biases and study limitations identified and discussed?	9.2	Yes
10 Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Unclear
10.1 Were sources of funding and investigators' affiliations described?	10.1	No
10.2 Was there no apparent conflict of interest?	10.2	Yes

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.

NEUTRAL (∅)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.

PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Appendix 2 Excluded Articles with Reason

Excluded Articles	**Reason for Exclusion**
Abbas, W., Rao, R. R., Agarwal, A., Saha, R., Bajpai, P., Qureshi, S., & Mittal, A. (2018). Incidence of Neuropathy with Weekly Paclitaxel and Role of Oral Glutamine Supplementation for Prevention of Paclitaxel Induced Peripheral Neuropathy Randomized Controlled Trial. *Indian Journal of Medical & Paediatric Oncology, 39*(3), 339–348. https://doi.org/10.4103/ijmpo.ijmpo_38_17	Not OM
Akbaş, S., Karabulut, E., Bozkurt, A. P. S., Aydın, Ö., Düzgün, D. E., & Güngör, G. (2018). Glutaminin Travmatik Oral Mukozal Lezyonların İyileşmesi Üzerine Etkileri; Deneysel Çalışma. *Journal of Academic Research in Medicine, 8*(3), 1–23. https://doi.org/10.5152/jarem.2018.2008	Animal Research
Arfons, L., & Lazarus, H. (2005). Total parenteral nutrition and hematopoietic stem cell transplantation: an expensive placebo? *Bone Marrow Transplantation*, *36*(4), 281–288.	Not HNC
Alonso Pérez, L., Fernández Vázquez, A., Valero Zanuy, M., Gomis Muñoz, P., León Sanz, M., & Herreros de Tejada, A. (2010). Parenteral nutrition supplemented with glutamine in patients undergoing bone marrow transplantation. *Nutrición Hospitalaria*, *25*(1), 49–52. Retrieved from https://doaj.org/article/3045040538214993a7a2707aaf84c33f	Parenteral glutamine Not HNC
Anderson, P., Ramsay, N., Shu, X., Rydholm, N., Rogosheske, J., Nicklow, R., … Skubitz, K. (1998). Effect of low-dose oral glutamine on painful stomatitis during bone marrow transplantation. *Bone Marrow Transplantation*, *22*(4), 339–344. https://doi.org/10.1038/sj.bmt.1701317	Not HNC
Andrade, M. E. R., Araújo, R. S., de Barros, P. A. V., Soares, A. D. N., Abrantes, F. A., Generoso, S. de V., Fernandes, S. O. A., & Cardoso, V. N. (2015). The role of immunomodulators on intestinal barrier homeostasis in experimental models. *Clinical Nutrition, 34*(6), 1080–1087. https://doi.org/10.1016/j.clnu.2015.01.012	Not glutamine
Aquino, V., Harvey, A., Garvin, J., Godder, K., Nieder, M., Adams, R., … Sandler, E. (2005). A double-blind randomized placebo-controlled study of oral glutamine in the prevention of mucositis in children undergoing hematopoietic stem cell transplantation: a pediatric blood and marrow transplant consortium study. *Bone Marrow Transplantation*, *36*(7), 611–616. https://doi.org/10.1038/sj.bmt.1705084	Pediatric population Not HNC
Araújo, C., Lazzarotto, C., Aquino, C., Figueiredo, I., Costa, T., Alves, L., … Oriá, R. (2015). Alanyl-glutamine attenuates 5-fluorouracil-induced intestinal mucositis in apolipoprotein E-deficient mice. *Brazilian Journal of Medical and Biological Research*, *48*(6), 493–501. https://doi.org/10.1590/1414-431X20144360	Not RT
Azevedo, O., Oliveira, R., Oliveira, B., Zaja-Milatovic, S., Araújo, C., Wong, D., … Oriá, R. (2012). Apolipoprotein E COG 133 mimetic peptide	Not RT

improves 5-fluorouracil-induced intestinal mucositis. *BMC Gastroenterology*, *12*, 35. https://doi.org/10.1186/1471-230X-12-35	
Ben-Arye, E., Polliack, A., Schiff, E., Tadmor, T., & Samuels, N. (2013). Advising patients on the use of non-herbal nutritional supplements during cancer therapy: a need for doctor-patient communication. *Journal of Pain and Symptom Management*, *46*(6), 887–896. https://doi.org/10.1016/j.jpainsymman.2013.02.010	Review article
Beutheu, S., Ouelaa, W., Guérin, C., Belmonte, L., Aziz, M., Tennoune, N., Bôle-Feysot, C., Galas, L., Déchelotte, P., & Coëffier, M. (2014). Glutamine supplementation, but not combined glutamine and arginine supplementation, improves gut barrier function during chemotherapy-induced intestinal mucositis in rats. *Clinical Nutrition, 33*(4), 694–701. https://doi.org/10.1016/j.clnu.2013.09.003	Animal Research
Blijlevens, N., Donnelly, J., Naber, A., Schattenberg, A., & Depauw, B. (2005). A randomised, double-blinded, placebo-controlled, pilot study of parenteral glutamine for allogeneic stem cell transplant patients. *Supportive Care in Cancer*, *13*(10), 790–796. https://doi.org/10.1007/s00520-005-0790-y	Not HNC
Bockel, S., Vallard, A., Lévy, A., François, S., Bourdis, M., Le Gallic, C. … Chargari, C. (2018). Pharmacological modulation of radiation-induced oral mucosal complications. *Cancer Radiotherapie : Journal de La Societe Francaise de Radiotherapie Oncologique, 22*(5), 429–437. https://doi.org/10.1016/j.canrad.2017.11.006	Review article
Boukhettala, N., Ibrahim, A., Claeyssens, S., Faure, M., Le Pessot, F., Vuichoud, J., … Coëffier, M. (2010). A diet containing whey protein, glutamine, and TGFbeta modulates gut protein metabolism during chemotherapy-induced mucositis in rats. *Digestive Diseases and Sciences, 55*(8), 2172–2181. https://doi.org/10.1007/s10620-009-1039-2	Animal research
Bowen, J., Gibson, R., Coller, J., Blijlevens, N., Bossi, P., Al-Dasooqi, N., …Elad, S. (2019) . Systematic review of agents for the management of cancer treatment-related gastrointestinal mucositis and clinical practice guidelines. Supportive Care in Cancer, 27(10), 4011–4022. https://doi.org/10.1007/s00520-019-04892-0	Systematic Review
Burdak-Rothkamm, S., Smith, A., Lobachevsky, P., Martin, R., & Prise, K. (2015). Radioprotection of targeted and bystander cells by methylproamine. *Strahlentherapie Und Onkologie*, *191*(3), 248–255. https://doi.org/10.1007/s00066-014-0751-9	Not glutamine
Carl, W., & Havens, J. (2000). The cancer patient with severe mucositis. *Current Review of Pain, 4*(3), 197–202.	Review
Cerchietti, L., Navigante, A., Lutteral, M., Castro, M., Kirchuk, R., Bonomi, M., … Uchima, P. (2006). Double-blinded, placebo-controlled trial on intravenous l-alanyl- l-glutamine in the incidence of oral mucositis following chemoradiotherapy in patients with head-and-neck cancer. International Journal of Radiation Oncology, Biology, Physics, 65(5), 1330–1337. https://doi.org/10.1016/j.ijrobp.2006.03.042	Parenteral Glutamine

Chang, S., Lai, Y., Hung, J., & Chang, C. (2019). Oral glutamine supplements reduce concurrent chemoradiotherapy-induced esophagitis in patients with advanced non-small cell lung cancer. *Medicine*, *98*(8). https://doi.org/10.1097/MD.0000000000014463	Not HNC
Chang, Y., Yu, M., Wu, K., Hsu, M., Chiou, Y., Wu, H., … Chao, Y. (2017). Effectiveness of Parenteral Glutamine on Methotrexate-induced Oral Mucositis in Children with Acute Lymphoblastic Leukemia. *Nutrition and Cancer, 69*(5), 746–751. https://doi.org/10.1080/01635581.2017.1324995	Pediatric population Chemotherapy not RT Parenteral glutamine
Chaveli-López, B., & Bagán-Sebastián, J. (2016). Treatment of oral mucositis due to chemotherapy. *Journal of Clinical and Experimental Dentistry, 8*(2), e201–9. https://doi.org/10.4317/jced.52917	Review article Chemotherapy not RT
Chen, H., Zhang, F., Li, R., Liu, Y., Wang, X., Zhang, X., … Yao, Q. (2020). Berberine regulates fecal metabolites to ameliorate 5-fluorouracil induced intestinal mucositis through modulating gut microbiota. *Biomedicine & Pharmacotherapy, 124*, N.PAG. https://doi.org/10.1016/j.biopha.2020.109829	Not RT
Chen, M., Wu, I., Chen, Y., Wang, T., Chang, Y., Yang, C., … Chu, C. (2018). Nutrition therapy in esophageal cancer-Consensus statement of the Gastroenterological Society of Taiwan. *Diseases of the Esophagus : Official Journal of the International Society for Diseases of the Esophagus*, *31*(8). https://doi.org/10.1093/dote/doy016	Not HNC
Cheng, J. (2000). Appropriate endpoint of mucositis and correct statistical method for the drug effect interpretation. *International Journal of Radiation Oncology, Biology, Physics*, *48*(3), 909–910.	Not a primary research study
Choi, K., Lee, S. S., Oh, S. J., Lim, S. Y., Lim, S. Y., Jeon, W. K., …. Kim, J. W. (2007). The effect of oral glutamine on 5-fluorouracil/leucovorin-induced mucositis/stomatitis assessed by intestinal permeability test. *Clinical Nutrition, 26*(1), 57–62.	Not XRT
Cho, Y., Hong, S., Jeon, S., Namgung, H., Lee, E., Lee, E., & Bang, S. (2019). Efficacy of parenteral glutamine supplementation in adult hematopoietic stem cell transplantation patients. *Blood Research, 54*(1), 23–30. https://doi.org/10.5045/br.2019.54.1.23	Not HNC
Clarkson, J. E., Worthington, H. V., & Eden, O. B. (2003). Interventions for preventing oral mucositis for patients with cancer receiving treatment. *The Cochrane Database of Systematic Reviews*, 3, CD000978.	Review
Cockerham, M. B., Weinberger, B. B., & Lerchie, S. B. (2000). Oral glutamine for the prevention of oral mucositis associated with high-dose paclitaxel and melphalan for autologous bone marrow transplantation. *The Annals of Pharmacotherapy, 34(*3), 300–303.	Not HNC Not XRT

Crowther, M., Avenell, A., & Culligan, D. (2009). Systematic review and meta-analyses of studies of glutamine supplementation in haematopoietic stem cell transplantation. *Bone Marrow Transplantation*, *44*(7), 413–425. https://doi.org/10.1038/bmt.2009.41	Not HNC Review article
de Menêses, A. G., Normando, A. G. C., Porto de Toledo, I., Reis, P. E. D., & Guerra, E. N. S. (2020). Effects of oral supplementation in the management of oral mucositis in cancer patients: A meta-analysis of randomized clinical trials. *Journal of Oral Pathology & Medicine, 49*(2), 117–125. https://doi.org/10.1111/jop.12901	Meta-analysis
Duncan, M., & Grant, G. (2003). Oral and intestinal mucositis - causes and possible treatments. *Alimentary Pharmacology & Therapeutics, 18*(9), 853–874.	Not primary research
Fukui, T., Itoh, Y., Orihara, M., Yoshizawa, K., Takeda, H., Kawada, S., & Yoshioka, T. (2011). [Elental prevented and reduced oral mucositis during chemotherapy in patients esophageal cancer]. Gan to Kagaku Ryoho. *Cancer & Chemotherapy, 38*(13), 2597–2601.	Not HNC
Gabriel, D. A., Shea, T., Olajida, O., Serody, J. S., & Comeau, T. (2003). The effect of oral mucositis on morbidity and mortality in bone marrow transplant. *Seminars in Oncology, 30*(6 Suppl 18), 76–83.	Review Not HNC
Garee, A., Termuhlen, A., Skeens, M., Rosselet, R., & Ryan-Wenger, N. (2009). The Efficacy of Oral Glutamine as a Preloaded Medicine in Reducing the Severity and Duration of Mucositis in the Pediatric Stem Cell Transplant Setting. *Biology of Blood and Marrow Transplantation*, *15*(2), 31–31. https://doi.org/10.1016/j.bbmt.2008.12.094	Not HNC Pediatric population
Gibson, R., Keefe, D., Lalla, R., Bateman, E., Blijlevens, N., Fijlstra, M., … Bowen, J. (2013). Systematic review of agents for the management of gastrointestinal mucositis in cancer patients. *Supportive Care in Cancer*, *21*(1), 313–326. https://doi.org/10.1007/s00520-012-1644-z	Systematic review
Gaurav, K., Goel, R., Shukla, M., & Pandey, M. (2012). Glutamine: A novel approach to chemotherapy-induced toxicity. *Indian Journal of Medical and Paediatric Oncology*, *33*(1), 13–20. https://doi.org/10.4103/0971-5851.96962	Not RT
Gómez Alvarez, M. E. (2004). Parenteral nutrition in hematopoietic stem cell transplantation. *Farmacia Hospitalaria : Organo Oficial de Expresion Cientifica de La Sociedad Espanola de Farmacia Hospitalaria*, 28(2), 116–122.	Not HNC
Greenlee, H., Hershman, D. L., & Jacobson, J. S. (2009). Use of antioxidant supplements during breast cancer treatment: a comprehensive review. *Breast Cancer Research and Treatment, 115*(3), 437–452. https://doi.org/10.1007/s10549-008-0193-0	Not HNC
Hansen, L., Smythe, P., Hansen, K., Gruenberg, D., & Callaway, D. (2006). Glutamine supplementation to reduce oral mucositis in multiple myeloma patients receiving high-dose melphalan and autologous stem cell transplantation: A feasibility study. *Biology of Blood and Marrow Transplantation*, *12*(2), 144–144. https://doi.org/10.1016/j.bbmt.2005.11.441	Not HNC

Harada, K., Ferdous, T., Kobayashi, H., & Ueyama, Y. (2018). Elemental Diet Accelerates the Recovery From Oral Mucositis and Dermatitis Induced by 5-Fluorouracil Through the Induction of Fibroblast Growth Factor 2. *Integrative Cancer Therapies*, *17*(2), 423–430. https://doi.org/10.1177/1534735417721014	Not RT Used elemental diet in addition to glutamine
Harsha, W. T. F., Kalandarova, E., McNutt, P., Irwin, R., & Noel, J. (2006). Nutritional supplementation with transforming growth factor-beta, glutamine, and short chain fatty acids minimizes methotrexate-induced injury. *Journal of Pediatric Gastroenterology and Nutrition, 42*(1), 53–58.	Pediatric research
Hernández, M., Solórzano, M., Rodríguez, F., Nieto, V. & Veintimilla, D. (2018). Intravenous glutamine does not modify leucocyte count but shortens duration of mucositis after bone marrow transplant. *Jounal of Negative and No Positive Results*, *3*(4), 279–287. https://doi.org/10.19230/jonnpr.2251	Parenteral glutamine Not HNC
Herrera-Martínez, A., Alhambra Expósito, M., Manzano García, G., Molina Puertas, M., Calañas Continente, A., Bahamondez Opazo, R., … Gálvez Moreno, M. (2015). Use of glutamine in total parenteral nutrition of bone marrow transplant patients. *Nutricion hospitalaria*, *31*(4), 1620–1624. https://doi.org/10.3305/nh.2015.31.4.8410	Not HNC Parenteral glutamine
Ibáñez, J., Ángel, B., & Gironzini, V. (2013). Best oral presentation: Prevention of mucositis in head and neck cancer (HNC) with glutamine. *Reports of Practical Oncology & Radiotherapy*, *18*(S1), S110–S110. https://doi.org/10.1016/j.rpor.2013.03.839	Different publication of an included study
Iyama, S., Sato, T., Tatsumi, H., Hashimoto, A., Tatekoshi, A., Kamihara, Y., … Kato, J. (2014). Efficacy of Enteral Supplementation Enriched with Glutamine, Fiber, and Oligosaccharide on Mucosal Injury following Hematopoietic Stem Cell Transplantation. *Case Reports in Oncology*, *7*(3), 692–699. https://doi.org/10.1159/000368714	Not HNC
Izaola, O., de Luis, D., Cuellar, L., Terroba, M., Ventosa, M., Martin, T., & Aller, R. (2010). Influence of an immuno-enhanced formula in postsurgical ambulatory patients with head and neck cancer. *Nutricion Hospitalaria*, *25*(5), 793–796. https://doi.org/10.3305/nh.2010.25.5.4529	Arginine in addition to glutamine Not all received RT
Jebb, S., Osborne, R., Maughan, T., Mohideen, N., Mack, P., Mort, D., … Elia, M. (1994). 5-fluorouracil and folinic acid-induced mucositis: no effect of oral glutamine supplementation. *British Journal of Cancer*, *70*(4), 732–735. https://doi.org/10.1038/bjc.1994.385	Not RT
Jolfaie, N., Mirzaie, S., Ghiasvand, R., Askari, G., & Miraghajani, M. (2015). The effect of glutamine intake on complications of colorectal and colon cancer treatment: A systematic review. *Journal of Research in Medical Sciences : the Official Journal of Isfahan University of*	Review article Not HNC

Medical Sciences, *20*(9), 910–918. https://doi.org/10.4103/1735-1995.170634	
Kalender, N., Tosun, N., & Arpacı, F. (2009). P0292 Comparison of the Effectiveness of Glutamine and Triple Gargle for Prevention of Mucositis Development in Patients Who Have Undergone Bone Marrow Transplantation. *European Journal of Internal Medicine, 20*, S102. https://doi.org/10.1016/S0953-6205(09)60312-5	Not HNC
Kanuga, S. (2013). Cryotherapy and keratinocyte growth factor may be beneficial in preventing oral mucositis in patients with cancer, and sucralfate is effective in reducing its severity. *Journal of the American Dental Association, 144*(8), 928–929. https://doi.org/10.14219/jada.archive.2013.0211	Not glutamine
Keefe, D. M., Schubert, M. M., Elting, L. S., Sonis, S. T., Epstein, J. B., Raber-Durlacher, J. E., … Peterson, D. E. (2007). Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer, 109*(5), 820–831.	Not a primary article
Keefe, D. M., Sonis, S. T., & Bowen, J. M. (2008). Emerging drugs for chemotherapy-induced mucositis. *Expert Opinion on Emerging Drugs, 13(*3), 511–522. https://doi.org/10.1517/14728214.13.3.511	Review Not RT
Knox, J. J., Puodziunas, A. L. V., & Feld, R. (2000). Chemotherapy-Induced Oral Mucositis: Prevention and Management. *Drugs & Aging, 17*(4), 257–267. https://doi.org/10.2165/00002512-200017040-00002	Not primary research
Kucher, M. A., Goloshchapov, O. V., Ganapiev, A. A., & Afanas'ev, B. V. (2010). [Use of various nutritional support regimens in patients with transplanted hematopoietic stem cells]. *Terapevticheskii Arkhiv, 82*(12), 43–47.	Not HNC
Kuskonmaz, B., Yalcin, S., Kucukbayrak, O., Cetin, N., Cetin, M., Tezcan, I., & Uckan, D. (2008). The effect of glutamine supplementation on hematopoietic stem cell transplant outcome in children: A case–control study. *Pediatric Transplantation*, *12*(1), 47–51. https://doi.org/10.1111/j.1399-3046.2007.00776.x	Pediatric population Not HNC
Lee, H., Huang, C., Huang, M., Chen, F., Wang, Y., Chen, C., … Wang, Y. (2018). Randomized Double-Blind, Placebo-Controlled Phase III trial Evaluating the Effect of Oral Glutamine on Radiation-Induced Oral Mucositis and Neck Dermatitis in Head and Neck Cancer Patients. *International Journal of Radiation Oncology, Biology, Physics*, *102*(3), e298–e298. https://doi.org/10.1016/j.ijrobp.2018.07.940	Different publication of an included study
Leggett, S., Koczwara, B., & Miller, M. (2015). The impact of complementary and alternative medicines on cancer symptoms, treatment side effects, quality of life, and survival in women with breast cancer--a systematic review. *Nutrition and Cancer*, *67*(3), 373–391. https://doi.org/10.1080/01635581.2015.1004731	Systematic review Not HNC
Leitão, R. F. C., Ribeiro, R. A., Lira, A. M. S., Silva, L. R., Bellaguarda, E. A. L., Macedo, F. D. B., … Brito, G. A. C. (2008). Glutamine and alanyl-glutamine accelerate the recovery from 5-fluorouracil-induced	Animal research

experimental oral mucositis in hamster. *Cancer Chemotherapy and Pharmacology, 61*(2), 215–222.	
Leung, H., & Chan, A. (2016). Glutamine in Alleviation of Radiation-Induced Severe Oral Mucositis: A Meta-Analysis. *Nutrition and Cancer*, *68*(5), 734–742. https://doi.org/10.1080/01635581.2016.1159700	Meta-analysis
Luna, J., Amaya, E., de Torres, M., Peña, M., & Prieto, I. (2015). Nutrients and Radiotherapy; Reviw of the Literature.. *Nutricion hospitalaria*, *32*(6), 2446–2459. https://doi.org/10.3305/nh.2015.32.6.9596	Review article
Maiguma, T., Kaji, H., Makino, K., & Teshima, D. (2009). Protective Effects of Amifostine and Cyclooxygenase-1 Inhibitor against Normal Human Epidermal Keratinocyte Toxicity Induced by Methotrexate and 5-Fluorouracil. *Basic & Clinical Pharmacology & Toxicology*, *105*(1), 1–9. https://doi.org/10.1111/j.1742-7843.2009.00400.x	Not RT
Manzi, N. de M., Silveira, R. C. de C. P., & dos Reis, P. E. D. (2016). Prophylaxis for mucositis induced by ambulatory chemotherapy: systematic review. *Journal of Advanced Nursing, 72*(4), 735–746. https://doi.org/10.1111/jan.12867	Not RT or HNC
Menêses, A. G., Normando, A. G. C., Porto de Toledo, I., Reis, P. E. D., Guerra, E. N. S., & de Menêses, A. G. (2020). Effects of oral supplementation in the management of oral mucositis in cancer patients: A meta-analysis of randomized clinical trials. *Journal of Oral Pathology & Medicine, 49*(2), 117–125. https://doi.org/10.1111/jop.12901	Meta-analysis
Mesejo Arizmendi, A., Ordóñez González, J., & Ortiz Leyba, C. (2005). Artificial nutrition in hematopoietic stem cells transplantation. *Nutricion hospitalaria*, *20 Suppl 2*, 54–56.	Not HNC
Metin, S., & Dere, H. (2017). Hematopoetik Kök Hücre Nakli ve Güncel Beslenme Yaklaşımları. *Türkiye Klinikleri Pediatri, 26*(1), 22–31. https://doi.org/10.5336/pediatr.2016-52429	Not HNC
Mirea, D., Niţipir, C., Barna, M., Mirea, L., Safta, D., Mocanu, B., … Berteşteanu, Ş. (2015). Impactul suplimentării orale cu glutamină asupra calităţii vieţii la pacienţii cu cancere de cap şi gât în cursul radioterapiei. *ORL.Ro*, 8(29), 42–46.	Not in English
Murray, S. M., & Pindoria, S. (2009). Nutrition support for bone marrow transplant patients. *The Cochrane Database of Systematic Reviews*, 1, CD002920. https://doi.org/10.1002/14651858.CD002920.pub3	Not HNC
Muscaritoli, M., Grieco, G., Capria, S., Iori, A., & Fanelli, F. (2002). Nutritional and metabolic support in patients undergoing bone marrow transplantation. *American Journal of Clinical Nutrition*, *75*(2), 183–190. https://doi.org/10.1093/ajcn/75.2.183	Not HNC Review article
Nihei, S., Sato, J., Komatsu, H., Ishida, K., Kimura, T., Tomita, T., & Kudo, K. (2018). The efficacy of sodium azulene sulfonate L-glutamine for managing chemotherapy-induced oral mucositis in cancer patients: a prospective comparative study.(Report). *Journal of Pharmaceutical Health Care and Sciences*, *4*(1), 20. https://doi.org/10.1186/s40780-018-0114-2	Not RT

Noé, J. (2009). L-glutamine use in the treatment and prevention of mucositis and cachexia: a naturopathic perspective. *Integrative Cancer Therapies*, *8*(4), 409–415. https://doi.org/10.1177/1534735409348865	Review article
Obayashi, Y., Kajiwara, K., & Nakamura, E. (2018). The Effect of Cisplatin on Blood Ammonia Elevation by Alanyl-Glutamine Supplementation. *Pharmacology, 101*(3/4), 156–162. https://doi.org/10.1159/000485919	Not RT
Ogata, Y., Takeuchi, M., Ishibashi, N., Kibe, S., Takahashi, K., Uchida, S., … Shirouzu, K. (2012). Efficacy of Elental on prevention for chemotherapy-induced oral mucositis in colorectal cancer patients. Gan to Kagaku Ryoho. *Cancer & Chemotherapy, 39*(4), 583–587.	Not HNC
Oliva García, J., Pereyra-García Castro, F., Suárez Llanos, J., Ríos Rull, P., Breña Atienza, J., & Palacio Abizanda, J. (2012). Efficacy of parenteral glutamine in patients undergoing bone marrow transplantation. *Nutricion hospitalaria*, *27*(1), 205–208. https://doi.org/10.1590/S0212-16112012000100025	Not HNC
Papadopoulou, A. (1998). Nutritional considerations in children undergoing bone marrow transplantation. *European Journal of Clinical Nutrition*, *52*(12), 863–871. https://doi.org/10.1038/sj.ejcn.1600669	Not HNC
Papanikolopoulou, A., Syrigos, K., & Drakoulis, N. (2015). The role of glutamine supplementation in thoracic and upper aerodigestive malignancies. *Nutrition and Cancer*, *67*(2), 231–237. https://doi.org/10.1080/01635581.2015.990572	Review article
Patel, A., Rajesh, S., Chandrashekhar, V., Rathnam, S., Shah, K., Mallikarjuna Rao, C., & Nandakumar, K. (2013). A rat model against chemotherapy plus radiation-induced oral mucositis. *Saudi Pharmaceutical Journal, 21*(4), 399–403. https://doi.org/10.1016/j.jsps.2012.11.003	Animal study
Pareek, V., Bhalavat, R., & Chandra, M. (2017). EP-1045: L Glutamine in reducing severity of oral mucositis due to chemoradiation in head and neck cancer. *Radiotherapy & Oncology, 123*, S577. https://doi.org/10.1016/S0167-8140(17)31481-0	Only abstract available
Peterson, D. E., Jones, J. B., & Petit, R. G., 2nd. (2007). Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. *Cancer, 109*(2), 322–331.	Not HNC
Peterson, D. E. (2006). New strategies for management of oral mucositis in cancer patients. *The Journal of Supportive Oncology, 4*(2 Suppl 1), 9–13.	Not a primary study
Piccirillo, N., De Matteis, S., Laurenti, L., Chiusolo, P., Sorà, F., Pittiruti, M., … Sica, S. (2003). Glutamine-enriched parenteral nutrition after autologous peripheral blood stem cell transplantation: effects on immune reconstitution and mucositis. *Haematologica*, *88*(2), 192–200.	Not HNC
Pietrobom, C., Honicky, M., Saciloto, M., Cavagnari, M., Zattar, J., Nodari, C., & Melhem, A. (2019). Evaluation of the frequency of food intake and the maintenance of the effect of glutamine supplementation on the	Pediatric population

attenuation of symptoms of moderate asthma in children, post wash out. *Nutrition & Health*, *14*(1). https://doi.org/10.12957/demetra.2019.37946	
Pytlík, R., Benes, P., Patorková, M., Chocenská, E., Gregora, E., Procházka, B., & Kozák, T. (2002). Standardized parenteral alanyl-glutamine dipeptide supplementation is not beneficial in autologous transplant patients: a randomized, double-blind, placebo controlled study. *Bone Marrow Transplantation*, *30*(12), 953–961. https://doi.org/10.1038/sj.bmt.1703759	Not HNC
Qutob, A. F., Gue, S., Revesz, T., Logan, R. M., & Keefe, D. (2013). Prevention of oral mucositis in children receiving cancer therapy: a systematic review and evidence-based analysis. *Oral Oncology, 49*(2), 102–107. https://doi.org/10.1016/j.oraloncology.2012.08.008	Pediatric research
Richards, D. (2006). Prevention of oral mucositis in cancer patients treated with chemotherapy or radiotherapy. *Evidence-Based Dentistry, 7*(4), 106.	Meta-analysis
Richardson, M., Martel, L., & Martensson, L. (2007). Outpatient transfusion practice and factors leading to inpatient transfusion in a pediatric hematology/oncology program. *Journal of Pediatric Oncology Nursing : Official Journal of the Association of Pediatric Oncology Nurses, 24*(1), 46–51.	Not HNC
Rosenthal, D. I., & Trotti, A. (2009). Strategies for managing radiation-induced mucositis in head and neck cancer. *Seminars in Radiation Oncology, 19(*1), 29–34. https://doi.org/10.1016/j.semradonc.2008.09.006	Review
Rubio, I., Cao, Y., Hutchins, L., Westbrook, K., & Klimberg, V. (1998). Effect of glutamine on methotrexate efficacy and toxicity. *Annals of Surgery*, *227*(5), 772–778. https://doi.org/10.1097/00000658-199805000-00018	Not RT
Ruiz-Esquide, G., Nervi, B., Vargas, A., & Maíz, A. (2011). [Treatment and prevention of cancer treatment related oral mucositis]. *Revista Medica de Chile, 139*(3), 373–381. https://doi.org//S0034-98872011000300015	Review article
Saadeh, C. E. (2005). Chemotherapy- and radiotherapy-induced oral mucositis: review of preventive strategies and treatment. *Pharmacotherapy, 25*(4), 540–554.	Review
Samuels, N., Schiff, E., & Ben-Arye, E. (2014). Non-herbal nutritional supplements for symptom relief in adjuvant breast cancer: creating a doctor-patient dialogue. *BMJ Supportive & Palliative Care*, *4*(3), e1. https://doi.org/10.1136/bmjspcare-2013-000463	Not HNC
Sangild, P., Shen, R., Pontoppidan, P., & Rathe, M. (2018). Animal models of chemotherapy-induced mucositis: translational relevance and challenges. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, *314*(2), G231–G246. https://doi.org/10.1152/ajpgi.00204.2017	Animal research
Sayles, C., Hickerson, S. C., Bhat, R. R., Hall, J., Garey, K. W., & Trivedi, M. V. (2016). Oral Glutamine in Preventing Treatment-Related Mucositis in	Systematic Review

Adult Patients With Cancer: A Systematic Review. *Nutrition in Clinical Practice : Official Publication of the American Society for Parenteral and Enteral Nutrition, 31*(2), 171–179. https://doi.org/10.1177/0884533615611857	
Sessle, B. J. (2011). Peripheral and central mechanisms of orofacial inflammatory pain. *International Review of Neurobiology, 97*, 179–206. https://doi.org/10.1016/B978-0-12-385198-7.00007-2	Review
Sharma, R., Tobin, P., & Clarke, S. J. (2005). Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhoea. *The Lancet. Oncology, 6*(2), 93–102.	Review Not RT
Silverman, S., Jr. (2007). Diagnosis and management of oral mucositis. *The Journal of Supportive Oncology, 5*(2 Suppl 1), 13–21.	Review
Sonis, S. T. (2006). Can oral glutamine prevent mucositis in children undergoing hematopoietic stem-cell transplantation? *Nature Clinical Practice. Oncology, 3*(5), 244–245.	Not HNC
Sornsuvit, C., Komindr, S., Chuncharunee, S., Wanikiat, P., Archararit, N., & Santanirand, P. (2008). Pilot Study: effects of parenteral glutamine dipeptide supplementation on neutrophil functions and prevention of chemotherapy-induced side-effects in acute myeloid leukaemia patients. *The Journal of International Medical Research, 36*(6), 1383–1391.	Not HNC
Stokman, M. A., Spijkervet, F. K. L., Boezen, H. M., Schouten, J. P., Roodenburg, J. L. N., & de Vries, E. G. E. (2006). Preventive intervention possibilities in radiotherapy- and chemotherapy-induced oral mucositis: results of meta-analyses. Journal of Dental Research, 85(8), 690–700.	Meta-analysis
Storey, B. (2007). The role of oral glutamine in pediatric bone marrow transplant. *Journal of Pediatric Oncology Nursing : Official Journal of the Association of Pediatric Oncology Nurses, 24*(1), 41–45.	Not HNC
Stubbe, C., & Valero, M. (2013). Complementary strategies for the management of radiation therapy side effects. *Journal of the Advanced Practitioner in Oncology*, *4*(4), 219–231.	Review article
Sukhotnik, I., Mogilner, J. G., Karry, R., Shamian, B., Lurie, M., Kokhanovsky, N., … Coran, A. G. (2009). Effect of oral glutamine on enterocyte turnover during methotrexate-induced mucositis in rats. *Digestion, 79*(1), 5–13. https://doi.org/10.1159/000191209	Animal research
Sukhotnik, I., Pollak, Y., Coran, A., Pilatov, J., Bejar, J., Mogilner, J., & Berkowitz, D. (2014). Glutamine attenuates the inhibitory effect of methotrexate on TLR signaling during intestinal chemotherapy-induced mucositis in a rat. *Nutrition & Metabolism*, *11*(1), 17. https://doi.org/10.1186/1743-7075-11-17	Animal research
Sun, W., Su, J., Shen, Z., & Hsu, H. (2018). 運用實證探討口服麩醯胺對癌症病人接受化學治療引起的周邊神經病變之成效. *Hu Li Za Zhi*, *65*(1), 61–69. https://doi.org/10.6224/JN.201802_65(1).09	Not in English Not RT

Tanaka, Y., Takahashi, T., Yamaguchi, K., Osada, S., Shimokawa, T., & Yoshida, K. (2016). Elemental diet plus glutamine for the prevention of mucositis in esophageal cancer patients receiving chemotherapy: a feasibility study. *Supportive Care in Cancer*, *24*(2), 933–941. https://doi.org/10.1007/s00520-015-2864-9	Elemental diet in addition to glutamine Not HNC
Thomsen, M., & Vitetta, L. (2018). Adjunctive Treatments for the Prevention of Chemotherapy- and Radiotherapy-Induced Mucositis. *Integrative Cancer Therapies, 17*(4), 1027–1047. https://doi.org/10.1177/1534735418794885	Literature review
Tort, S., & Acartürk, F. (2016). Preparation and characterization of electrospun nanofibers containing glutamine. *Carbohydrate Polymers, 152*, 802–814. https://doi.org/10.1016/j.carbpol.2016.07.028	Not HNC
Tydeman-Edwards, R. (2017). Glutamine and its use in selected oncology settings. *South African Journal of Clinical Nutrition*, *30*(4), 109–117. https://doi.org/10.1080/16070658.2017.1371467	Review article
Uderzo, C., Rebora, P., Marrocco, E., Varotto, S., Cichello, F., Bonetti, M., …. Cesaro, S. (2011). Glutamine-enriched nutrition does not reduce mucosal morbidity or complications after stem-cell transplantation for childhood malignancies: a prospective randomized study. *Transplantation, 91*(12), 1321–1325. https://doi.org/10.1097/TP.0b013e31821ab959	Pediatric research Not HNC
Ward, E., Picton, S., Reid, U., Thomas, D., Gardener, C., Smith, M., … Allgar, V. (2003). Oral glutamine in paediatric oncology patients: a dose finding study.(Original Communication). *European Journal of Clinical Nutrition*, *57*(1), 31–316. https://doi.org/10.1038/sj.ejcn.1601517	Pediatric population
Ward, E., Smith, M., Henderson, M., Reid, U., Lewis, I., Kinsey, S., … Picton, S. (2009). The effect of high-dose enteral glutamine on the incidence and severity of mucositis in paediatric oncology patients. *European Journal of Clinical Nutrition*, *63*(1), 134–140. https://doi.org/10.1038/sj.ejcn.1602894	Pediatric population
Worthington, H. V., Clarkson, J. E., Bryan, G., Furness, S., Glenny, A.-M., Littlewood, A., … Khalid, T. (2011). Interventions for preventing oral mucositis for patients with cancer receiving treatment. *The Cochrane Database of Systematic Reviews, 4*, CD000978. https://doi.org/10.1002/14651858.CD000978.pub5	Meta-analysis
Wright, J., Feld, R., & Knox, J. (2005). Chemotherapy-induced oral mucositis: new approaches to prevention and management. *Expert Opinion on Drug Safety, 4*(2), 193–200.	Not a primary study Not RT
Yarom, N., Ariyawardana, A., Hovan, A., Barasch, A., Jarvis, V., Jensen, S., … Lalla, R. (2013). Systematic review of natural agents for the management of oral mucositis in cancer patients. *Supportive Care in Cancer : Official Journal of the Multinational Association of*	Review article

Supportive Care in Cancer, *21*(11), 3209–3221. https://doi.org/10.1007/s00520-013-1869-5	
Yavas, C., Yavas, G., Acar, H., Toy, H., Yuce, D., Akyurek, S., & Ata, O. (2013). Amelioration of radiation-induced acute inflammation and mucosal atrophy by beta-hydroxy-beta-methylbutyrate, L-glutamine, and L-arginine: results of an experimental study.(Clinical report). *Supportive Care in Cancer*, *21*(3).	Animal study
Yildirim, Z. K., Bidev, D., & Buyukavci, M. (2013). Parenteral glutamine supplementation has no effect on chemotherapy-induced toxicity in children with non-Hodgkin lymphoma. *Journal of Pediatric Hematology/Oncology, 35*(5), 371–376. https://doi.org/10.1097/MPH.0b013e318282daf4	Not HNC Parenteral glutamine
Yokota, T., Hamauchi, S., Yoshida, Y., Yurikusa, T., Suzuki, M., Yamashita, A., … Onitsuka, T. (2018). A phase II study of HMB/Arg/Gln against oral mucositis induced by chemoradiotherapy for patients with head and neck cancer. *Supportive Care in Cancer*, *26*(9), 3241–3248. https://doi.org/10.1007/s00520-018-4175-4	Other supplements besides glutamine
Yuce Sari, S., Yazici, G., Yuce, D., Karabulut, E., Cengiz, M., & Ozyigit, G. (2016). The effect of glutamine and arginine-enriched nutritional support on quality of life in head and neck cancer patients treated with IMRT. *Clinical Nutrition ESPEN, 16*, 30–35. https://doi.org/10.1016/j.clnesp.2016.08.003	Additional supplements besides glutamine, different outcome measures

Appendix 3 Tally Sheet of Quality Criteria Checklists

	Vidal-Casariego et al., 2013	*Akmansu et al., 2018*	*P□chon Ibanez et al., 2018*	*E. Huang et al., 2000*	*Chattopadhyay et al., 2014*	*Pathak et al., 2019*	*Pattanayak et al., 2016*	*Tsujimoto et al., 2015*	*C. Huang et al., 2019*	*Lopez-Vaquero et al., 2019*
Overall Quality Rating	Ø	Ø	Ø	+	Ø	Ø	Ø	+	Ø	+
Relevance Questions										
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	YES	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	YES	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	YES	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
Validity Questions										
1. Was the research question clearly stated?	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
2. Was the selection of study subjects/patients free from bias?	NO	NO	Unclear	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
3. Were study groups comparable?	*Unclear*	*Unclear*	*Unclear*	YES	YES	*Unclear*	*Unclear*	YES	*YES*	*YES*
4. Was method of handling withdrawals described?	N/A	N/A	NO	NO	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
5. Was blinding used to prevent introduction of bias?	NO	NO	NO	*YES*	NO	NO	NO	*YES*	*YES*	*YES*
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	NO	NO	NO	*YES*	Unclear	NO	*YES*	*YES*	Unclear	*YES*
7. Were outcomes clearly defined and the measurements valid and reliable	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
8. Was the statistical analysis appropriate for the study design and type of outcome indicators?	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
9. Are conclusions supported by results with biases and limitations taken into consideration?	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	NO	*YES*	*YES*
10. Is bias due to study's funding or sponsorship unlikely?	Unclear	Unclear	Unclear	Unclear	Unclear	*YES*	Unclear	*Unclear*	*YES*	*Unclear*