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BestPractice

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# Prevention And Treatment Of Oral Mucositis In Cancer Patients

## Introduction

Oral mucositis, also called stomatitis, is a common, debilitating complication of cancer chemo-therapy and radiotherapy, occurring in about 40% of patients. It results from the systemic effects of cytotoxic chemotherapy agents and from the local effects of radiation to the oral mucosa. Oral mucositis is inflammation of the mucosa of the mouth which ranges from redness to severe ulceration. Symptoms of mucositis vary from pain and discomfort to an inability to tolerate food or fluids. Mucositis may also limit the patient's ability to tolerate either chemotherapy or radiotherapy. Mucositis may be so severe as to delay treatment and so limit the effectiveness of cancer therapy. Patients with damaged oral mucosa and reduced immunity resulting from chemotherapy and radiotherapy are also prone to opportunistic infections in the mouth. The mucositis may affect patients' gum and dental condition, speech and self esteem are reduced, further compromising patients' response to treatment and/or palliative care.

It is therefore extremely important that mucositis be prevented whenever possible, or at least treated to reduce its severity and possible complications.

Currently there is a bewildering number of interventions to choose from, but no high quality synthesis of the best research evidence for these interventions. This Best Practice Information Sheet has been developed to present the best available evidence related specifically to the prevention and treatment of oral mucositis induced by chemotherapy or radiotherapy in cancer patients. The information presented in this document is based on a systematic review undertaken by The Joanna Briggs Institute for Evidence Based Nursing and Midwifery.

This Practice Information Sheet Covers The Following Concepts

1. Quality Of Research
2. Treatment Options
3. What Is Effective
4. Recommendations - Oral Care Protocol
5. Other Treatment Options

### Levels of Evidence

All studies were categorised according to the strength of the evidence based on the following classification system.

- **Level I**
  Evidence obtained from a systematic review of all relevant randomised controlled trials.
- **Level II**
  Evidence obtained from at least one properly designed randomised controlled trial.
- **Level III.1**
  Evidence obtained from well designed controlled trials without randomisation.
- **Level III.2**
  Evidence obtained from well designed cohort or case control analytic studies preferably from more than one centre or research group.
- **Level III.3**
  Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments.
- **Level IV**
  Opinion of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

## Quality Of Research

The systematic review of the research literature identified a vast number of interventions that have been investigated to determine their effectiveness in the prevention or treatment of oral mucositis in cancer patients. It is obvious that many interventions used in clinical practice have never been rigorously evaluated. Furthermore, many combinations of agents are advocated by local experts without evidence to support their use. The quality of published papers was variable, and although a large number of experimental studies were identified, some were rejected due to deficiencies in study design or in reporting. Combining results from different studies during the systematic review and meta-analysis was limited mostly because of differences between the study participants', interventions, and the timing and method of measuring outcomes.

While many interventions used for the treatment or prevention of mucositis have some evidence supporting their use, no intervention has been conclusively validated by research. Consequently, the recommendations in this information sheet have been based on research findings and supplemented by expert clinical opinion.

## Treatment Options

Many different treatments are used to prevent or treat mucositis. To aid the discussion of findings these interventions have been categorised under the following headings;

- general oral care protocols;
- interventions to reduce the mucosal toxicity of chemotherapy drugs;
- mouthwashes with mixed action;
- immunomodulatory agents;
- topical anaesthetics;
- antiseptics;
- antibacterial, antifungal and antiviral agents
- mucosal barriers and coating agents;
- cytoprotectants;
- mucosal cell stimulants;
- psychotherapy; and
- analgesics.

### Oral Care Protocols

Much has been written about oral care regimens and many discussion papers have reported locally developed regimens. These regimens typically include dental work to eliminate caries and existing gum disease before beginning cancer treatment, followed by thorough and frequent cleaning of the oral cavity with a variety of products, some form of pain relief, anti-inflammatory treatment as required and aggressive antimicrobial treatment for any new mouth infections. However there have been very few experimental studies designed to test the effectiveness of particular oral care protocols. It should also be noted that most of the specific interventions for mucositis prevention and treatment reviewed below were tested against a background of good oral care. There appears to be broad support for some form of oral care protocol as a commonsense preventive measure, but further research is required to optimise specific oral care regimens.

### Interventions Which Reduce The Mucosal Toxicity Of Chemotherapy Drugs

The interventions used to minimise mucosal toxicity include allopurinol and cryotherapy. Allopurinol mouthwashes 4 to 6 times per day have been evaluated as prophylaxis against mucositis resulting specifically from the action of 5-fluorouracil chemotherapy. Results of the meta-analysis support the use of allopurinol mouthwash to prevent mucositis.

Cryotherapy, or rapid cooling of the oral cavity using ice, causes local vasoconstriction and hence reduces blood flow to the oral mucosa. For cytotoxic and neoplastic drugs such as 5-fluorouracil, which have a short half life and are sometimes administered as a bolus injection, cryotherapy may reduce the amount of drug reaching the oral mucous membranes, and may therefore reduce mucositis caused by local cytotoxic activity of these drugs. Studies support the use of cryotherapy as a cheap and effective method of minimising mucositis induced by bolus 5-fluorouracil, but it is not effective for continuous infusions.

### Mouthwashes With Mixed Actions

A variety of mouthwashes with mixed actions have been evaluated and include benzydamine hydrochloride, corticosteroids and chamomile. Benzydamine hydrochloride is a drug which has anti-inflammatory, pain relieving, antipyretic and antimicrobial activities, and has been used as a gargle or mouthwash to prevent and treat oral mucositis. There is good evidence that benzydamine hydrochloride mouthwash is effective in improving the symptoms of radiation-induced mucositis in patients with head and neck cancer. However, further work is needed to evaluate the effectiveness of this agent for chemotherapy-induced mucositis, and to compare benzydamine with other pre-parations.

Chamomile is said to have anti-inflammatory and spasmolytic effects and to promote mucosal healing, however there is no evidence to support its use. Corticosteroids have also been used in mouthwash preparations as treatment for mucositis and there is limited evidence in favour of corticosteroid mouthwash.

### Immunomodulatory Agents

The effectiveness of colony stimulating factors and immunoglobulin have been evaluated. Granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) are cytokines which stimulate haemopoiesis and modulate leukocyte functions. No beneficial effect has been demonstrated with a mouthwash containing GM-CSF, but the results of a small study suggest G-CSF administered subcutaneously may be effective in preventing and reducing the duration of mucositis. It has been suggested that administration of human immunoglobulin might confer passive immunity to immuno-compromised patients and so reduce the severity of mucositis. While there is some evidence to support its use for patients with head and neck cancer undergoing chemo/radiotherapy it has not been shown to be effective in patients undergoing radiation therapy alone.

### Topical Anaesthetics

Topical anaesthetic agents have been included as part of some oral care protocols, but their effectiveness has rarely been evaluated. Viscous lignocaine and xylocaine in mouth rinses have been recommended for patients whose oral mucositis pain is severe, but currently there is no evidence to support their use. Comparisons between dyclonine HC1, viscous lignocaine with 1% cocaine and a solution containing kaolin-pectin, diphenhydramine and saline, found dyclonine provided better pain relief.

### Antiseptics

A range of antiseptic solutions have been used including chlorhexidine, povidone iodine and hydrogen peroxide. Chlorhexidine is perhaps one of the most commonly used mouthwash solutions identified in studies and has been used as prophylaxis for both chemotherapy and radiotherapy induced mucositis. However, the evidence does not support its use, indeed it has been suggested that water mouthwashes are as effective as chlorhexidine.

A single uncontrolled study was identified which examined the use of a povidone iodine gargle for preventing mucositis in patients with leukaemia. Two studies evaluating hydrogen peroxide mouth rinses in cancer patients concluded that systematic oral care may be more important than the specific mouth rinsing agent used. There is currently no evidence to support the use of either povidone iodine or hydrogen peroxide mouthwash.

### Antibacterial, Antifungal And Antiviral Agents

Many oral care regimens include prophylactic antibacterial and/or antifungal treatments to clear the mouth of oral microflora before and during chemo/radiotherapy. Antimicrobial agents used include nystatin, clotrimazole and PTA lozenges. Nystatin is a broad spectrum antifungal agent, and comparison between nystatin mouthwash, saline or placebo failed to show any significant difference in mucositis severity or oral ulceration score. Clotrimazole alone, or in combination with polymixin B and tobramycin has been evaluated, and while one study suggests it is more effective than chlorhexidine, issues of methodological quality of these studies make it difficult to draw firm conclusions.

Antibiotic lozenges designed to dissolve in the mouth and decontaminate the oral mucosa have been developed and have been widely recommended to reduce oral infections associated with mucositis. The lozenges contain polymixin E, tobramycin and amphotericin B, which together provide broad spectrum antibacterial and antifungal cover. These are commonly known as PTA lozenges or PTA pastilles. There is some evidence supporting the use of PTA lozenges in preventing infectious complications of mucositis in cancer patients undergoing radiotherapy, but there is as yet no evidence relating to their efficacy in chemotherapy treated patients.

Acyclovir is an antiviral agent which is active against the *Herpes* species that commonly infect the oral mucous membranes in immunosuppressed cancer patients. It appears that prophylactic acyclovir may have some value in reducing oral lesions due to *Herpes* in susceptible patients, but as the majority of mucositis lesions do not result from a virus they are not affected by this agent.

## Mucosal Barriers And Coating Agents

A variety of agents have been used to act as a mucosal barrier, with sucralfate subject to the most study. Sucralfate is a sulfated disaccharide which is not absorbed, but binds electrostatically to gastric ulcers, acting as a barrier to irritants and promoting healing. It has been suggested that sucralfate may also protect oral mucosal surfaces in patients at risk of developing mucositis, but the available evidence does not support its use.

A number of other agents acting as mucosal barriers have been promoted as possible strategies for preventing or minimising chemo/radiotherapy induced mucositis. These include sodium alginate, kaolin-pectin, plastic wrap film, radiation guards and antacid. However none of these have been rigorously tested in clinical trials, and so no comments about their relative efficacy can be made.

## Cytoprotectants

Beta-carotene (pro-vitamin A), vitamin E and oxpentifylline have cytoprotective properties and have been used in cancer patients in an attempt to ameliorate the mucositis resulting from cytotoxic treatments, but currently there is no evidence to support their use. Azelastine hydrochloride has membrane stabilising and leukocyte suppressing activities and one study evaluating the effectiveness of 2mg/day throughout cytotoxic treatment suggests it significantly reduces the duration and severity of mucositis. Prostaglandins E1 and E2 have many activities, including cytoprotective actions. While early observational and pilot studies of the effectiveness of local application of prostaglandins were promising, the evidence does not support its use, and indeed, prostaglandin E may exacerbate mucositis in these patients.

## Mucosal Cell Stimulants

Low energy laser treatment may promote the proliferation of mucosal cells and wound healing, and has been tried as a treatment for chemo/radiotherapy-induced mucositis. The limited evidence available supports its use in bone marrow transplant patients, but more research is required for non-transplant cancer patients. Silver nitrate has also been used to stimulate the mucosal epithelial cells to proliferate, but the available evidence suggests that silver nitrate is of questionable value in preventing radiation-induced mucositis. Glutamine, which is a major energy source for mucosal epithelial cells and stimulates mucosal growth and repair, has been evaluated and the limited available evidence suggests that it may decrease the duration of mucositis, although further research is required.

## Psychotherapy

Psychological interventions for managing persistent cancer pain have been advocated as adjuncts to pharmacological techniques, but little work has been done to evaluate these interventions. Psychotherapy techniques tested include cognitive behaviour training, relaxation and imagery training, hypnosis and therapist support. Hypnosis reduced oral pain experienced by patients, but intake of opioid analgesics was not significantly different. Relaxation and imagery training significantly reduced patient-assessed mucositis pain, but the reductions in pain were not matched by corresponding reductions in mucositis severity or intake of opioids for oral pain relief.

## Analgesics

Patients undergoing bone marrow transplantation usually develop severe mucositis requiring aggressive analgesia with intravenous opioids. A modification of patient controlled analgesia, where individual pharmacokinetic profiles for morphine were used to tailor the infusion rates for each patient, was compared to traditional patient controlled bolus analgesia. The pharmacokinetically based patient controlled analgesia was superior to conventional patient controlled analgesia in terms of relief of oral mucositis pain, and even though more morphine was used by the former group there were no increases in the side effects of morphine. A further trial was conducted by the same research group to compare the opioids morphine with alfentanil using this system and morphine was significantly more potent than alfentanil for pain relief.

Capsaicin, which is the active ingredient in chilli peppers and acts by desensitising some neurones to provide temporary pain relief, has also been evaluated. Candies containing capsaicin have been promoted as an alternate analgesic treatment for chemotherapy-induced mucositis. Currently, there is insufficient evidence to draw conclusions about the possible benefits of capsaicin candy.

# Recommendations - Oral Care Protocol

All patients at risk of developing mucositis should receive a standardised oral care regime as an ongoing component of their care. The aim of this regimen is to achieve and maintain a clean mouth and to limit opportunistic infection via the damaged mucosa. This information is based on Level IV evidence (expert opinion).

### 1) Mucositis Assessment

Assess condition of the patient's mouth daily. While there is no evidence to suggest any one assessment tool is better than others, below is the World Health Organisation grading of mucositis as an example of a typical tool.

| Grade | Signs And Symptoms |
|---|---|
| 0 | No symptoms |
| 1 | Sore mouth, no ulcers |
| 2 | Sore mouth with ulcers, but able to eat normally |
| 3 | Liquid diet only |
| 4 | Unable to eat or drink |

### 2) Before Commencement Of Therapy

Interventions that may be beneficial prior to the commencement of treatment include:

- treatment of caries and dental disease; and
- education regarding the importance of orodental hygiene, how to maintain oral hygiene and to develop a daily routine of oral care.

### 3) Post Therapy

Interventions that may be beneficial following treatment include:

- clean teeth and gums after meals and before sleep with tooth brush or swab as tolerated;
- rinse the mouth regularly;
- if dentures are worn, remove and clean them daily and leave out while at rest;
- avoid painful stimuli such as hot food and drinks, spicy food, alcohol and smoking;
- regular inspection of mouth by the patient and health professionals;
- report any redness, tenderness or sores on the lips or in mouth;
- provide comfort measures such as lubrication of the lips, topical anaesthesia and analgesics;
- prompt treatment of mucositis symptoms and oral infections.

# Other Treatment Options

In addition to the use of an oral care protocol, the following interventions may offer some benefits. It should be noted that the support for some of these interventions is based on limited Level II evidence, and with further research these findings may change. Some of these products are currently not available in Australia.

**1) For patients with head and neck cancer and undergoing radiotherapy:**

**a)** Prevention of Mucositis
- benzydamine
- PTA lozenges

**b)** Treatment of Mucositis Symptoms
- benzydamine
- dyclonine HCL

**2) Patients receiving chemotherapy, with or without radiotherapy:**

**a)** Prevention of Mucositis
- allopurinol for patients treated with 5-fluorouracil
- cryotherapy for patients treated with 5-fluorouracil boluses

**b)** Treatment of Mucositis Symptoms
- topical dyclonine or lignocaine

**3) For patients undergoing high dose chemotherapy for bone marrow transplantation:**
- patient controlled administration of opioids tailored to individual patient needs for pain management.

## What Is Effective?

It is very difficult for the clinician to choose from this bewildering array of treatment options. It appears many interventions have little evidence supporting their effectiveness, while others have a small amount of evidence suggesting they may be effective. No intervention has been conclusively shown to be effective. Conversely, only prostaglandin E was shown to be potentially harmful in terms of mucositis in this group of patients.

This situation has arisen because of the proliferation of small studies that lack the power to adequately evaluate interventions. Contributing to this situation is the fact that few studies have been replicated, with each successive study utilising a different intervention, population or outcome measure. Finally, some studies failed to provide sufficient information regarding the research design, making assessment of quality impossible.

So what interventions appear to prevent or minimise the severity and duration of mucositis? There is some evidence to suggest that allopurinol and cryotherapy during boluses of 5-fluorouracil may reduce mucosal toxicity. The evidence supports mouthwashes containing benzydamine for reducing the effects of radiation induced mucositis. There is also limited evidence to support the use of mouthwashes containing corticosteroids. While subcutaneous G-CSF appears to be effective, mouthwashes containing GM-CSF are not. Intramuscular immunoglobulin reduced the severity of mucositis in patients receiving chemo-radiotherapy, but not in those receiving radiotherapy alone. In terms of topical anaesthetic agents, dyclonine appears to provide better pain relief than lignocaine or diphenhydramine. PTA lozenges appear to minimise infectious complications in radiotherapy patients, but its usefulness in chemotherapy is uncertain. Azelastine may reduce the duration and severity of mucositis. There is limited evidence to suggest low energy laser may be effective in bone marrow transplant patients. Glutamine may reduce the duration of mucositis. Hypnosis and relaxation and imagery therapy reduced the pain experienced by patients, but not the use of analgesics or mucositis severity. Morphine administered by patient controlled analgesia appears to be effective for reducing mucositis pain

## What Interventions Do Not Have Evidence To Support Their Use?

While chlorhexidine is commonly recommended and used, its effectiveness remains uncertain. Sucralfate has been the subject of many studies, however its effectiveness has yet to be shown. There is no evidence to support the use of beta-carotene or vitamin E, and prostaglandin E may well exacerbate mucositis, Silver nitrate is not supported and as a result of insufficient evidence it is impossible to evaluate the effectiveness of capsaicin.

As there are no interventions that have conclusively been shown to be effective, the following recommendations for the prevention and management of oral mucositis are based on available evidence and supplemented by the opinion of clinical experts.


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- Nursing Directors
- Specialist Cancer Nurses
- Pharmacist
- Dentist
- Haematologist
- Oncologist

This publication was produced based on a systematic review of the research literature undertaken by The Joanna Briggs Institute under the guidance of a review panel of clinical experts. It has been subject to peer review by experts nominated by The Joanna Briggs Institute centres throughout Australia, New Zealand and Hong Kong and was led by Dr. Inge Kowanko – The Joanna Briggs Institute; Mr. Brent Hodgkinson - The Joanna Briggs Institute; Dr Lesley Long - Royal Adelaide Hospital; Mr David Evans - The Joanna Briggs Institute.



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