Interventions for preventing oral mucositis for patients with cancer receiving treatment

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Clarkson JE, Worthington HV, Eden OB

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Interventions for preventing oral mucositis for patients with cancer receiving treatment (Review)

Clarkson JE, Worthington HV, Eden OB

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ABSTRACT

Background
Treatment of cancer is increasingly more effective but is associated with short and long term side effects. Oral side effects remain a major source of illness despite the use of a variety of agents to prevent them. One of these side effects is oral mucositis (mouth ulcers).

Objectives
To evaluate the effectiveness of prophylactic agents for oral mucositis in patients with cancer receiving treatment, compared with other potentially active interventions, placebo or no treatment.

Search strategy
The Cochrane Oral Health Group’s Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE were searched. Reference lists from relevant articles were scanned and the authors of eligible studies were contacted to identify trials and obtain additional information.
Date of most recent searches June 2002.

Selection criteria
Trials were selected if they met the following criteria: design - random allocation of participants; participants - anyone with cancer receiving chemotherapy or radiotherapy treatment for cancer; interventions - agents prescribed to prevent oral mucositis; outcomes - prevention of mucositis, pain, amount of analgesia, dysphagia, systemic infection, length of hospitalisation, cost and patient quality of life.

Data collection and analysis
Information regarding methods, participants, interventions and outcome measures and results were independently extracted, in duplicate, by two reviewers. Authors were contacted for details of randomisation and withdrawals and a quality assessment was carried out. The Cochrane Oral Health Group statistical guidelines were followed and relative risk values calculated using random effects models.

Main results
One hundred and nine studies were eligible. Fifty-seven were excluded for various reasons, usually as there was no useable information on mucositis. Of the 52 useable studies all had data for mucositis comprising 3594 randomised patients. Interventions evaluated were: acyclovir, allopurinol mouthrinse, amifostine, antibiotic pastille or paste, benzydamine, camomile, chlorhexidine, clarithromycin, folinic acid, glutamine, GM-CSF, hydrolytic enzymes, ice chips, oral care, pentoxifyline, povidone, prednisone, propantheline, prostaglandin, sucralfate and traumeel. Of the 21 interventions included in trials, nine showed some evidence of a benefit (albeit sometimes weak) for either preventing or reducing the severity of mucositis. Interventions where there was more than one trial and a significant difference compared with a placebo or no treatment were allopurinol with unreliable evidence for a reduction in the severity of mucositis OR = 0.01 (95% CI: 0 to 0.03), amifostine provided minimal benefit in preventing mucositis RR = 0.95 (95% CI: 0.91 to 0.99), antibiotic paste or pastille demonstrated a moderate benefit in preventing mucositis RR = 0.87 (95% CI: 0.79 to 0.97), GM-CSF prevented mucositis RR = 0.51 (95% CI: 0.29 to 0.91), hydrolytic enzymes reduced the severity of mucositis RR = 0.49 (95% CI: 0.30 to 0.81),
and ice chips prevented mucositis OR = 0.42 (95% CI: 0.19 to 0.93). Other interventions showing some benefit with only one study were: benzydamine, oral care protocols and povidone.

The NNT to prevent one patient experiencing mucositis over a baseline incidence of 60% for amifostine is 33 (95% CI: 20 to 100), antibiotic paste or pastille 13 (95% CI: 8 to 50), GM-CSF 3 (95% CI: 2 to 20) and ice chips 5 (95% CI: 2 to 31). When the baseline incidence is 40%/90% the NNTs for amifostine are 50/20, for antibiotic paste or pastille 20/8, for GM-CSF 5/2 and for ice chips 6/10.

The general reporting of RCTs was poor. However, the quality of the randomisation improved when the authors provided additional information.

Authors’ conclusions
Several of the interventions were found to have some benefit at preventing or reducing the severity of mucositis associated with cancer treatment. The strength of the evidence was variable and implications for practice include consideration that benefits may be specific for certain cancer types and treatment. There is a need for well designed and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent.

PLAIN LANGUAGE SUMMARY
Several therapies appear to either prevent or reduce the severity of mouth ulcers caused by chemotherapy or radiotherapy for cancer.

Treatment for cancer (including bone marrow transplant) can cause oral mucositis (severe ulcers in the mouth). This can cause discomfort, pain, difficulties in eating, and a longer stay in hospital. Different strategies are used to try and prevent this condition, and the review of trials found that some of these are effective. Effective treatments include several drugs which can be taken as tablets and others which can be added to the cancer treatment regimen. Other interventions that were effective were a mouthwash medicated with allopurinol and sucking ice chips before and during the cancer treatment.

BACKGROUND
Treatment of solid malignant tumours and the leukaemias with cytotoxic chemotherapy and/or radiotherapy is becoming increasingly more effective but it is associated with short and long term side effects. Among the clinically important acute side effects is the disruption in the function and integrity of the mouth. The consequences of this include severe ulceration (mucositis) and fungal infection of the mouth (oral candidiasis, thrush). These disease and treatment induced complications may also produce oral discomfort and pain, poor nutrition, delays in drug administration, increased hospital stays and costs and in some patients life threatening infection (septicaemia).

Oral complications remain a major source of illness despite the use of a variety of agents to prevent them. There are variations in usage between cancer centres in terms of the mouthcare regimen used. Compliance with recommended use of product is variable and there are conflicting reports of the effectiveness of prophylactic agents. The qualitative and quantitative benefits, side effects and costs of oral therapies are of importance to the cancer teams responsible for the treatment of patients.

There have been several traditional reviews published and most of these present a general discussion for both chemotherapy and radiotherapy induced oral side effects (De Pauw 1997; Denning 1992; Lortholary 1997; Stevens 1995; Symonds 1998; Verdi 1993; White 1993). The conclusions drawn and recommendations made vary from advocating a particular therapy to recommending oral care procedures that have not been systematically investigated.

Two systematic reviews have focused on the prevention of oral mucositis in patients with cancer. One older review published in 1998 concluded that for most strategies reviewed there is insufficient evidence to draw any conclusions regarding their effectiveness (Kowanko 1998). The other more recent review focused on patients with head and neck cancer only and the main analysis combined all the interventions in one meta-analysis and found a beneficial effect of prophylactic interventions (Sunderland 2001).

A previous version of this Cochrane review looked at the use of oral and prophylactic agents for the prevention of oral mucositis and oral candidiasis in patients with cancer treated by chemotherapy (Clarkson 2003a). The review concluded that there was some evidence that using ice chips during the chemotherapy treatment was effective in preventing mucositis. This updated review broadens the oral mucositis part of that review and looks at the prevention of oral mucositis in patients receiving any treatment for cancer, including patients with all types of cancer, including head and neck cancer, and including comparisons between any
interventions for prevention. A second review updating the prevention of oral candidiasis has also been recently published on The Cochrane Library (Worthington 2003a). These reviews form part of a series of four Cochrane reviews on the prevention and treatment of oral mucositis and oral candidiasis (Clarkson 2003b; Worthington 2003b).

OBJECTIVES

To evaluate the effectiveness of interventions (which may include placebo or no treatment) for the prevention of oral mucositis in patients with cancer receiving chemotherapy and/or radiotherapy.

The following primary null hypothesis was tested for comparisons between groups receiving interventions to prevent oral mucositis during cancer treatment:

There is no difference in the proportion of patients acquiring oral mucositis during cancer treatment.

In this review we proposed to address the hypothesis of no difference between groups treated for oral mucositis for the following outcomes if data were available:

- Relief of pain
- Amount of analgesia
- Relief of dysphagia
- Incidence of systemic infection
- Days of stay in hospital
- Cost of oral care
- Patient quality of life.

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- Incidence of systemic infection
- Days of stay in hospital
- Cost of oral care
- Patient quality of life.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Oral Health Group methods used in reviews.

This review is part of a series of four reviews on the prevention and treatment of oral candidiasis and oral mucositis in patients with cancer, and the same search strategy was used for all four reviews.

The search attempted to identify all relevant trials irrespective of language. Papers not in English were translated by members of the Cochrane Collaboration.

Electronic searching - the databases searched were:

- The Cochrane Oral Health Group’s Trials Register (May 2002)
- The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2002)
- MEDLINE (from 1966 to May 2002)
- EMBASE (from 1974 to June 2002).

Sensitive search strategies were developed for each database (available from the authors on request) using a combination of free text and Mesh terms.

The search strategy for CENTRAL is given as an example below:

1. NEOPLASMS*:ME
2. LEUKEMIA*:ME
3. LYMPHOMA*:ME
4. RADIOThERAPY*:ME
5. BONE-MARROW-TRANSPLANTATION:ME
6. neoplasm*
7. cancer*
8. (leukemi* OR leukaemi*)
9. (tumour* OR tumor*)
10. malignan*
METHODS OF THE REVIEW

The titles and abstracts (when available) of all reports identified through the searches were scanned by two reviewers (Jan Clarkson (JC) and Helen Worthington (HW)). Full reports were obtained for trials appearing to meet the inclusion criteria, or for which there was insufficient information in the title and abstract to make a clear decision. The full reports obtained from all the electronic and other methods of searching were assessed independently, in duplicate, by these two reviewers to establish whether the trials met the inclusion criteria or not. Disagreements were resolved by discussion.

The quality assessment of included trials was undertaken independently and in duplicate by two reviewers as part of the data extraction process. Included trials were assessed on three criteria, concealed allocation of treatment (A = adequate, B = unclear, C = inadequate), blinding of patients (0 = no, 1 = yes, 2 = unclear), carers and outcome assessors (0 = no, 1 = yes, 2 = unclear), and information on reasons for withdrawal by trial group (0 = no, 1 = yes). The agreement between the reviewers was assessed by calculating the kappa score.

Data were extracted by two reviewers independently using specially designed data extraction forms. The characteristics of the trial participants, interventions and outcomes in the included trials are presented in the study tables. Mucositis may be dichotomised at different levels of severity. In order to maximise the availability of similar outcome data we recorded the number of patients in each category of mucositis. Pain was assessed on visual analogue scales (0 to 100), the means and standard deviations for each group were recorded. The duration of trials and timing of assessments were recorded in order to make a decision about which to include for commonality. We also recorded the country where the trial was conducted and whether a dentist was involved in the investigation. Some of the authors were contacted for clarification or for further information.

DATA SYNTHESIS

For dichotomous outcomes, the estimates of effect of an intervention were expressed as relative risks together with 95% confidence intervals, apart from meta-analyses including cross-over studies, where odds ratios were used.

We planned to investigate clinical heterogeneity by examining the different cancer types and age groups, however there were insufficient trials to undertake this. Meta-analyses were done only with studies of similar comparisons reporting the same mucositis outcome measures. Relative risks were combined for dichotomous data using random effects models. The significance of any discrepancies in the estimates of the treatment effects from the different trials was assessed by means of Cochran's test for heterogeneity.

CROSS-OVER TRIALS

The treatment effects from cross-over trials were combined with those from parallel group trials where appropriate, using the data from both periods of the cross-over studies. Stata was used for this analysis, outside RevMan (Elbourne 2002). Where data for the cross-tabulation of pairs was not available, all possible paired comparisons for each study were calculated. In situations where more than one data cross-tabulation was possible, the scenarios taking the most extreme cases were considered and incorporated into any meta-analysis.

It was planned to undertake a sensitivity analysis to examine the effect of concealed allocation and blind outcome assessment on the overall estimates of effect. However there were insufficient trials in any specific intervention group to undertake this.

We proposed a priori to conduct subgroup analyses for different cancer types (head and neck, other solid tumours, leukaemia and mixed) and age groups (children, adults and mixed). However there were insufficient trials by intervention type to do this.
DESCRIPTION OF STUDIES

CHARACTERISTICS OF THE TRIAL SETTINGS AND INVESTIGATORS
See ’Characteristics of included studies’ table.
See ’Characteristics of excluded studies’ table.

There were 109 trials eligible for inclusion in the review. Fifty-seven of these trials were excluded for the following reasons:


- mucositis data presented in the form of mean scores, which were not in an appropriate form for this review (23 trial reports: Apaydin 1996; Barash 1995; Bensadoun 1999; Cowen 1997; Dudjak 1987; Epstein 1989; Epstein 1992; Epstein 1994; Etiz 2000; Feber 1996; Grotz 2001; Hanson 1997; Jebb 1995; Kenny 1990; Lievens 1998; Lopez 1994; McGaw 1985; Prada 1985; Raether 1989; Rutkauskas 1993; Samaranayake 1988; Verdi 1995; Weisdorf 1989)

- mucositis data not in appropriate form for other reasons than that given above (eight trial reports: Anderson 1998b; Chi 1995; Decker-Baumann 1999; Epstein 1986; Epstein 2001; Nicholl 1995; Niibe 1985b; Vacha 1999)

- data presented as episodes rather than patients, where patients were re-entered into the study, so data not independent (two trials: Hickey 1982; Karthaus 1998)

- major change to protocol half way through study (one trial: Okuno 1997)

- investigation of new cancer treatment, where mucositis was minor side effect (one trial: Cunningham 1995)

- qualitative assessment of mucositis (one trial: McIlroy 1996)

- comparing different radiotherapy regimens (one trial: Falcone 2001)

- randomised controlled trial (RCT) design fault (two trials: Erkisi 1996; Rocke 1993)


Of the 52 included trials all included data on assessment of mucositis. Nineteen (37%) trials were conducted in USA or Canada, 21 (40%) in Europe, three trials in Japan, two in India and one in each of the following countries: Mexico, Taiwan, China, Turkey, Israel, Hong Kong and one multicentre study in the USA and European countries. Only two trials were multicentre that included patients in more than one country (Brizel 2000; Nemunaitis 1995). Thirty-one trials received external funding, with this being unclear in a further 11 trials and with no external funding evident in 10 trials. A dentist was involved in 14 of the trials and in six trials the patient was involved in the clinical outcome measure.

CHARACTERISTICS OF THE PARTICIPANTS

Forty-three (83%) of the included trials recruited only adult patients, seven included both adults and children (with a difference in age as large as 1-70 years), only one trial was conducted solely on paediatric patients (Shenep 1988) and the age range was unclear in one study (Mahood 1991). The type of cancer for which patients were being treated was exclusively head and neck cancer in 25 trials (48%), leukaemia in five trials, solid tumours in 10 trials and a combination of haematological and solid tumours in nine trials, the cancer type being unclear in three trials. The radiotherapy and/or chemotherapy regimen was described in most of the trials though the chemotherapeutic agents were not always described in full detail. Of the five trials involving patients treated for leukaemia three were studies involving patients receiving a bone marrow transplant and the corresponding figure for mixed cancers was five. The chemotherapy regimen included 5-FU in six of the 10 trials for patients with solid tumours although it was not always clear if the dose was in a bolus or continuous form. Trials in which patients received radiotherapy generally gave information about the total and daily or weekly dose. Total radiotherapy for head and neck cancer was generally 60-74 Gy and the Karnofsky performance > 60.

CHARACTERISTICS OF INTERVENTIONS

All of the 52 trials provided a clear description of the interventions including the dose and method of administration for the test and control group. The dosage of the test agents varied for similar products. All the trials used either a placebo (28 trials), a no treatment control (18 trials), or water (two trials), glycine, sugar solution, polycal, saline (one trial each) as a control group. Two trials included in the no treatment control group tested different oral care protocols and in each case one group received limited oral hygiene (Borowski 1994; Shieh 1997).

The interventions for the 52 studies assessing oral mucositis were:

- acyclovir (Bubley 1989)
- allopurinol mouthrinse (Dozono 1989; Loprinzi 1990)
- antibiotic pastille or paste (Symonds 1996; Wijers 2001)
CHARACTERISTICS OF OUTCOME MEASURES

Mucositis

All trials used a graded scale to record the severity of mucositis. Most described the index used or referred to published criteria, mainly WHO or EROTC. Scales were similar to the five point WHO scale ranging from 0 (normal) to 4 (severe). The categories initially relate to visible changes in the mucosa and gradually record pain and inability to eat solid foods. Thirty-four studies provided information for an absent versus present dichotomy, 29 trials provided information dichotomising at grade 1 and 30 trials dichotomising at grade 2. The duration of the trials varied from a few days up a year after treatment. The interval during which mucositis was recorded varied from 5 to 90 days or until the end of the radiotherapy, or the leukocyte count was above 8000 mm³. Several studies presented data at different time points, with the median time point being 28 days. The nearest assessment to 28 days was used for all studies.

There was little consistency on the other outcome measures reported:

- Oral hygiene measures (Borowski 1994; Wahlin 1989)
- Relief of pain (Carter 1999; Cengiz 1999; Franzen 1995; Pfeiffer 1990; Van der Leslie 2001; Wijers 2001)
- Use of analgesia (morphine) (Attal 1993; Carter 1999; Cengiz 1999; Ferretti 1988; Makko nen 2000; Van der Leslie 2001)
- Duration or severity of dysphagia (Antonadou 2002; Bourhis 2000; Buntzel 1998; Cengiz 1999; Franzen 1995; Gujral 2001; Pfeiffer 1990; Prada 1987; Symonds 1996)
- Use of parenteral nutrition or feeding tube (Bourhis 2000; Carter 1999; Carter 1999; Dickson 2000; Yuen 2001)
- Incidence of systemic infection or use of antibiotics (Attal 1993; Borowski 1994; Crawford 1999; Ferretti 1990; Shenep 1988; Van der Leslie 2001; Yuen 2001)
- Blood changes (Ahmed 1993; Antonadou 2002; Buntzel 1998; Carter 1995; Crawford 1999; Van der Leslie 2001)
- Treatment interruption (Antonadou 2002; Carter 1999; Makko nen 1994)
- Days of stay in hospital (Attal 1993; Dickson 2000; Duenas 1996; Van der Leslie 2001)
- Toxicity - nausea/vomiting/constipation/diarrhoea (Antonadou 2002; Bourhis 2000; Brizel 2000; Cengiz 1999; Dickson 2000; Duenas 1996; Labar 1993; Shenep 1988; Yuen 2001)
- Toxicity - skin changes (Bourhis 2000; Buntzel 1998; Buntzel 1998; Gujral 2001; Shenep 1988; Yuen 2001)
- Toxicity - unspecific (Fedler 1996; Makkonen 1994; Makkonen 2000; Okuno 1999)
- Xerostomia (Brizel 2000; Buntzel 1998; Cengiz 1999)
- Cost (Dodd 1996)
- Patient quality of life (no trials)
- Death (Ahmed 1993; Attal 1993; Brizel 2000; Ferretti 1988; Labar 1993; Makkonen 2000)

METHODOLOGICAL QUALITY

There was excellent agreement between the scores assigned by the two reviewers, with kappa values for concealment 0.88, patient blind 0.85, carer blind 0.90, outcome assessor blind 0.68 and clear description of withdrawals 0.72.

The results of the quality assessment for concealment of randomisation, blinding of outcome assessor and whether there is a clear explanation of drop outs by study group are given in ‘Additional Table 01’, using the criteria outlined in the methods section. Changes
in the quality assessment due to information from authors are shown by putting the initial assessment in parenthesis.

There was variation in the quality of the studies using the reported information and additional information provided by authors. Overall, 54% of the trials had adequate concealment of randomisation, in 58% the patient was blinded to treatment group, 52% the provider of treatment blinded, 60% the assessor blinded and in 63% adequate information of withdrawals was given with the reason specified by study group. Sixty per cent of trials (31/52) reported some external support and of these 19 acknowledged assistance from pharmaceutical companies. The quality of trials varied slightly in relation to funding with 68% of those funded having adequate allocation concealment compared with 33% in the unfunded trials (chi squared p-value = 0.015). However no other significant differences were found between funded and unfunded trials. Funded trials are more likely to use central randomisation by a statistician.

Twenty-four out of 44 (55%) investigators replied to our letters requesting further information and this changed the allocation concealment assessments from B to A in nine studies. Information provided about blinding and withdrawals changed the quality assessment scores for five trials and data were provided from four trials (Anderson 1998; Leborgne 1997; Loprinzi 1990; Mahood 1991).

RESULTS

109 reports of trials were initially identified as eligible according to the defined criteria for study design, participants, interventions and outcomes. The total number of included trials was 52; there were five duplicate reports and 57 studies were excluded, as the data presented were not in an accessible form for this review. See ‘Characteristics of excluded studies’ table for further information on this.

Of the 52 included studies all had data for mucositis appropriate for this review comprising 3594 randomised patients.

The interventions involving cross-over trials are allopurinol, glutamine, ice chips and sucralfate. As it was not possible to incorporate these trials using RevMan software, the data and analysis for these interventions appears in the ‘Additional Tables 2 to 4’. The remainder of the results section presents the results relating to each intervention in alphabetical order.

- Allopurinal versus placebo/no treatment (‘Additional Table 03 and Table 04’)

Two trials, both designed as cross-over studies, compared allopurinal mouthrinse with placebo or no treatment (Dozono 1989; Loprinzi 1990). The pooled meta-analyses at both mucositis 0 versus 1+, and 0-1 versus 2+ dichotomies were non-significant, however the dichotomy 0-2 versus 3+ gave rise to a significant odds ratio of approximately zero, (95% confidence interval (CI): 0, 0.03) which was based on 34 adults with solid tumors, suggesting that allopurinal may reduce severe mucositis, when compared with a placebo. Both trials had adequate concealment of allocation, one had a blinded outcome assessment and there were no drop outs in either trial.

- Amifostine versus placebo/no treatment (MetaView ‘Comparison 01’, ‘Outcome 01, 02, 03’)

Six trials compared amifostine with a placebo (Niibe 1985) or no treatment (Antonadou 2002, Bourhis 2000, Brizel 2000, Buntzel 1998, Koukourakis 2000). All trials recruited adults with head and neck cancer being treated with radiotherapy. Three trials provided data for mucositis at the level of 0 versus 1+, however, only one trial provided estimable data (Brizel 2000) because every patient experienced mucositis in the other two. There was a significant benefit for amifostine preventing mucositis in this trial with relative risk (RR) = 0.95 (95% CI: 0.91 to 0.99). At the dichotomy 0-1 versus 2+ one trial was significant (Brizel 2000) and in the pooled meta-analysis the five trials provided homogeneous data (Antonadou 2002; Bourhis 2000; Brizel 2000; Koukourakis 2000; Niibe 1985) demonstrating amifostine as more effective than placebo or no treatment at preventing mucositis RR = 0.83 (95% CI: 0.72 to 0.97, chi squared = 4.34, df = 3, p = 0.23). Two of the five trials providing data for the dichotomy of mucositis of 0-2 versus 3+ were significant (Antonadou 2002; Buntzel 1998) however, the pooled meta-analysis failed to reach significance (p = 0.07) and did not support amifostine as being more effective than no treatment at reducing the severity of mucositis RR = 0.54 (95% CI: 0.27 to 1.06, chi squared = 26.01, df = 4, p < 0.0001). This indicates that amifostine may prevent and reduce the severity of oral mucositis in adults with head and neck cancer treated with radiotherapy. This is based on evidence from five trials with 446 participants. In two of the trials the allocation concealment was adequate, none had a blinded outcome assessment and two had an adequate explanation of withdrawals, with withdrawals across the five trials ranging from 0% to 21%.

- Antibiotic pastille or paste versus placebo (MetaView ‘Comparison 01’, ‘Outcome 01, 02, 03’)

One trial compared antibiotic pastilles with a placebo (Symonds 1996) and one trial antibiotic paste PTA with a placebo (Wijers 2001). For the outcome of mucositis 0 versus 1+ the pooled meta-analysis for the topical antibiotics was homogeneous and significant with mucositis prevented RR = 0.87 (95% CI: 0.79 to 0.97).
For the other dichotomies there was no evidence that antibiotic paste was more effective than placebo. This finding indicated that topical antibiotic may be beneficial at preventing mucositis is based on evidence from 198 adults treated for head and neck cancer, one trial was double blind and both trials failed to give clear information about allocation concealment.

- Benzydamine versus placebo (MetaView 'Comparison 01', 'Outcome 01')

One trial compared benzydamine with a placebo (Prada 1987) and for the outcome of mucositis 0 versus 1+ there was evidence that it prevented mucositis compared to placebo RR = 0.67 (95% CI: 0.47 to 0.97). This finding is based on a single trial of only 36 participants and is therefore considered weak and unreliable evidence of a benefit.

- Camomile versus placebo (MetaView 'Comparison 01', 'Outcome 01, 02, 03')

One trial compared camomile with a placebo (Fidler 1996). Data were provided for all three dichotomies of mucositis. No statistically significant differences were found therefore there is insufficient evidence to support or refute camomile as more or less effective than placebo.

- Chlorhexidine versus placebo/no treatment (MetaView 'Comparison 01', 'Outcome 01, 02, 03')

Six trials compared chlorhexidine with either a placebo or no treatment control group. All trials provided data on the incidence of mucositis which could be dichotomised at some level, along the five point scale (0-4). Four trials (Dodd 1996; Ferretti 1988; Ferretti 1990; Foote 1994) provided data for the first dichotomy (0 versus 1-4), and there was no evidence that the chlorhexidine mouthrinse was more effective than placebo or no treatment control in preventing mucositis RR = 0.67 (95% CI: 0.33 to 1.36, chi squared = 30, df = 4, p < 0.001). Only one trial (Foote 1994) provided data comparing mucositis dichotomised as 0-1 versus 2+, and this was not significant, data from this trial failing to show a benefit for chlorhexidine. Three trials (Foote 1994; Spijkervet 1989; Wahlin 1989) provided data for the third dichotomy of mucositis 0-2 versus 3+ and once again this was not significant, with no benefit for chlorhexidine being demonstrated.

- Folinic acid versus no treatment (MetaView 'Comparison 01', 'Outcome 01, 02, 03')

One trial compared folinic acid with a no treatment control group (Erlichman 1988). Participants in the no treatment group were less likely to experience mucositis compared with those receiving folinic acid. This difference was statistically significant for the dichotomies of mucositis 0 versus 1+ RR = 3.65 (95% CI: 2.38 to 5.58) and mucositis 0-1 versus 2+, RR = 2.38 (95% CI: 1.35 to 4.21). This trial was published in 1988 and initially involved 130 patients receiving 5 FU chemotherapy for solid tumours. It was unclear if the assessor was blinded to the treatment group and information on withdrawals was not provided. It provides weak evidence that folinic acid might induce mucositis compared with no treatment. This would be expected as folinic acid potentiates 5 FU cytotoxic activity.

- Glutamine versus placebo ('Additional Table 02, Table 03 and Table 04')

Five trials, two of which had a cross-over design, included the intervention glutamine compared with placebo (Anderson 1998; Dickson 2000; Huang 2000; Jebb 1994; Okuno 1999). None of the meta-analyses found any significant differences between glutamine and placebo. Two trials provided data for the first dichotomy 0 versus 1-4, however as every patient developed mucositis in one trial (Huang 2000), only the results from the other trial (Okuno 1999) could be considered. This study did not demonstrate a benefit for glutamine when compared with placebo. Five trials (Anderson 1998; Dickson 2000; Huang 2000; Jebb 1994; Okuno 1999) provided data for the 0-1 versus 2-4 dichotomy and three of these for the 0-2 versus 3-4 dichotomy. The meta-analyses demonstrated no evidence that glutamine prevented mucositis formation at any level of severity.

- GM-CSF versus placebo/no treatment (MetaView 'Comparison 01', 'Outcome 01, 02, 03')

Seven trials compared GM-CSF with a placebo or no treatment control group. Five trials were placebo (Cartee 1995; Nemunaitis 1995, Van der Leslie 2001) two of which (Crawford 1999, Schneider 1999) compared filgrastim (recombinant human granulocyte colony stimulating factor) and two trials had a no treatment control group (Katano 1995, Makkonen 1994). Three trials provided data for the dichotomy of mucositis 0 versus 1+ (Crawford 1999; Katano 1995; Makkonen 1994) the meta-analysis was statistically significant with evidence that GM-CSF prevents mucositis RR = 0.51 (95% CI: 0.29 to 0.91, chi squared = 1.35, df = 1, p = 0.24). The data were homogeneous for the two contributing trials because in one trial every patient developed mucositis (Makkonen 1994). For the other dichotomies there was no evidence that GM-CSF was more effective than placebo or no treatment. Evidence for the benefit for GM-CSF is moderate based on two trials with data from 209 adults treated for solid tumours and in each study it was unclear if the assessor was blind. The absence of benefit at levels of mucositis other than absence or presence of mucositis suggests that it may prevent mucositis rather than reduce its severity.

- Hydrolytic enzymes versus no treatment (MetaView 'Comparison 01', 'Outcome 01, 02, 03')

One trial compared hydrolytic enzymes with a no treatment control group (Gujral 2001) and one compared wobe-mugos with a no treatment control group (Kaul 1999). Both trials provided data for each of the meta-analyses. Individually the trials were significant for different levels of mucositis. The pooled meta-analysis did not find a difference for the dichotomy of mucositis absent versus present, however, significant differences were found for mucositis
0-1 versus 2+ RR = 0.49 (95% CI: 0.30 to 0.81) and for mucositis 0-2 versus 3+, RR = 0.18 (95% CI: 0.06 to 0.53). For both of these comparisons the data were homogeneous, based on 149 adults treated for head and neck cancer in open trials, one with adequate allocation concealment and unclear information on withdrawals in both. The evidence suggests that hydrolytic enzymes may reduce the severity of mucositis associated the treatment of head and neck cancer rather than prevent it.

- Ice chips versus no treatment (‘Additional Table 02, Table 03 and Table 04’)

Two trials (Cascinu 1994; Mahood 1991), one of which was designed as a cross-over trial compared ice chips with a no treatment control group. Significant differences were found at the first two dichotomies of mucositis, with odds ratios of 0.42 (95% CI: 0.19 to 0.93) and 0.36 (95% CI: 0.15 to 0.89) for absent versus present and 0-1 versus 2+ respectively. The evidence is moderate from two trials with 166 patients treated with 5 FU chemotherapy. The quality of the reporting of the trials varied and neither had a blinded outcome assessment. This indicated that ice chips may be beneficial in preventing or reducing the severity of mucositis for patients treated with 5 FU.

- Oral care versus no treatment or limited oral hygiene (MetaView ‘Comparison 01’, ‘Outcome 01, 02, 03’)

Two trials compared oral care with no treatment or limited oral hygiene (Borowski 1994, Shiieh 1997) and reported outcomes at different levels of mucositis. A significant difference was found for oral care versus no treatment (Shieh 1997) at the level of mucositis 0 versus 1+ with a relative risk of 0.60 (95% CI: 0.42 to 0.86). The other trial did not find a significant difference between intensive and limited oral hygiene. This indicates that oral care interventions may be beneficial in preventing mucositis however the evidence is weak and based on a single study of 30 adults treated for head and neck cancer with radiotherapy. There was adequate concealment of allocation, no drop outs and the outcome assessor was blinded to treatment group.

- Pentoxifyline versus no treatment (MetaView ‘Comparison 01’, ‘Outcome 02’)

One trial compared pentoxifyline with a no treatment control group (Attal 1993). Data were provided at the dichotomy of mucositis 0-1 versus 2+. No statistically significant differences were found therefore there is insufficient evidence to support or refute that pentoxifyline is more or less effective than no treatment.

- Povidone versus water (MetaView ‘Comparison 01’, ‘Outcome 01, 02, 03’)

One trial compared povidone with water (Rahn 1997) and for each dichotomy of mucositis povidone was significantly more effective than water for mucositis 0 versus 1+, RR = 0.70 (95% CI: 0.53 to 0.93), mucositis 0-1 versus 2+ RR = 0.45 (95% CI: 0.28 to 0.73) and mucositis 0-2 versus 3+ RR = 0.31 (95% CI: 0.12 to 0.78). This indicates that povidone may be beneficial at preventing and reducing the severity of mucositis. The evidence is weak based on a single study of 40 adults treated for head and neck cancer with unclear concealment of allocation, no drop outs and blinded outcome assessment.

- Prednisone versus placebo (MetaView ‘Comparison 01’, ‘Outcome 01, 02, 03’)

One trial compared prednisolone with a placebo (Leborgne 1997). Data were provided at all three dichotomies of mucositis. No statistically significant differences were found and therefore there is insufficient evidence to support or refute that prednisone is more or less effective than placebo.

- Propatheline versus placebo (MetaView ‘Comparison 01’, ‘Outcome 01’)

One trial compared propatheline with a placebo (Ahmed 1993). Data were provided at the dichotomy of mucositis 0 versus 1+. No statistically significant differences were found and therefore there is insufficient evidence to support or refute that propatheline is more or less effective than placebo.

- Prostaglandin versus placebo (MetaView ‘Comparison 01’, ‘Outcome 01, 03’)

Two trials compared prostoglandin with a placebo (Duenas 1996, Labar 1993). Data were provided for two of the dichotomies of mucositis. No statistically significant differences were found and therefore there is insufficient evidence to support or refute that prostaglandin is more or less effective than placebo.

- Sucralfate versus placebo (‘Additional Table 02, Table 03 and Table 04’)

Six trials, one of which had a cross-over design (Pfeiffer 1990), compared the intervention sucralfate with a placebo (Carter 1999; Cengiz 1999; Franzen 1995; Makkonen 1994; Pfeiffer 1990; Shenep 1988). Data were provided at three dichotomies of mucositis. No statistically significant differences were found and therefore there is insufficient evidence to support or refute that sucralfate is more or less effective than placebo.

- Systemic antibiotic clarithromycin versus no treatment (MetaView ‘Comparison 01’, ‘Outcome 02’)

One trial compared clarithromycin with no treatment (Yuen 2001). Data were provided at the dichotomy of mucositis 0-1 versus 2+. The difference was on the borderline of statistical significance RR = 0.69 (95% CI: 0.48 to 1.01). This indicated that this systemic antibiotic may reduce the severity of mucositis and the results may be considered with those of topical antibiotics.

- Traumeel versus placebo (MetaView ‘Comparison 01’, ‘Outcome 01’)

One trial compared traumeel with a placebo (Oberbaum 2001). Data were provided at the dichotomy of mucositis 0 versus 1+. No
statistically significant difference was found and therefore there is insufficient evidence to support or refute that tramecul is more or less effective than placebo.

ADDITIONAL OUTCOMES
The information relating to additional outcomes and side effects was variable across the 52 included studies. To explore these further, for the interventions found to be beneficial at preventing or reducing the severity of mucositis data were pooled and synthesised for side effects relating to amifostine (Meta-analysis ‘Comparison 02’ ‘Outcome 01’) and GM-CSF (Meta-analysis ‘Comparison 02’ ‘Outcome 02’).

Of the six trials evaluating amifostine four reported seven side effects (Antonadou 2002; Brizel 2000; Bourhis 2000; Koukourakis 2000). For five of these, data from more than one study were available. No significant difference was found between amifostine and no treatment control for survival at 24 months, recurrence at 18 months after cancer treatment, incomplete response to radiotherapy, hypotension and nausea. Delay to radiotherapy was on the borderline of significance with those receiving amifostine less likely to have a delay to receiving radiotherapy for cancer however, it was based on a single study of 39 patients RR = 0.44 (95% CI: 0.19 to 1.01). The only significant finding was for vomiting with no patients in the control group compared with 10/182 treated with amifostine experiencing this side effect RR = 5.92 (95% CI: 1.03 to 33.91, chi squared = 1.01, df = 2, p = 0.6).

Of the seven trials evaluating GM-CSF only two provided useable data for side effects (Makkonen 2000; Nemunaitis 1995) and not the same side effect. No difference was found between patients receiving GM-CSF and no treatment control for survival at 24 months, survival at 12 months, relapse within 1 year or nausea. A significant difference was found for local skin reactions with patients receiving GM-CSF more likely to experience a rash RR = 27 (95% CI: 1.71 to 425).

NUMBER NEEDED TO TREAT
Numbers needed to treat (NNTs) have only been calculated for interventions with more than one study reporting mucositis at the level of absence versus present. The NNT to prevent one patient experiencing mucositis over a baseline incidence of 60% for amifostine is 33 (95% CI: 20 to 100), antibiotic paste or pastille 13 (95% CI: 8 to 50), GM-CSF 3 (95% CI: 2 to 20) and ice chips 5 (95% CI: 2 to 31). When baseline incidence is 40% or 90% the NNTs for amifostine are 50 and 20, for antibiotic paste or pastille 20 and 8, for GM-CSF 5 and 2 and for ice chips 6 and 10.

DISCUSSION
This review updates the evidence for interventions for the prevention of oral mucositis for patients receiving cancer treatment and includes considerably more evidence than the initial review (Clarkson 2003a). This is due to the inclusion of interventions for patients with head and neck cancer and the expansion of evidence in this area of cancer care. Oral mucositis is a common complication of cancer chemotherapy and radiotherapy causing severe pain and may limit the tolerability to chemotherapy and radiotherapy and consequently the effectiveness of treatment (Kowanko 1998).

The findings of this review should be considered in context with the general medical management of patients with cancer. Outcome measures, other than clinical scores for mucositis, were predominantly reported in recent publications. Rarely did they consider clinically meaningful outcomes such as oral pain, use of opioid analgesic, oral intake, quality of life, duration of hospital stay (Bellm 2002).

The number and range of interventions included in this review indicates the uncertainty and importance of this clinical topic. The 52 trials included in this review have evaluated 21 interventions and recruited 3594 patients. The country of conduct, financial support and the design of trials have varied. Surprisingly despite the common recruitment of patients into multicentre cancer treatment trials the same has not happened for their oral care. The two multicentre trials were the largest with respect to patient recruitment. The lack of duplication of studies investigating the same interventions limits the strength of evidence and generalisability.

The eligible trials for this review varied in their design and quality and it was especially unfortunate that 34 studies presented data in an unusable form. We feel that the use of structured abstracts and adherence to the CONSORT guidelines will greatly improve the reporting and hopefully the conduct of randomised controlled trials (RCTs) (Begg 1996; Moher 2001). With respect to publication bias, several negative studies for mucositis have been reported and we congratulate the authors and editors for doing so. It was not possible to detect any existing publication bias, as there were insufficient studies in each meta-analysis investigating the same interventions.

The setting of the included trials varied with the majority being conducted by medical teams who did not report any involvement with a dentist (73%). An issue that was not considered in any of the trials was the reliability and validity of the outcome measures assessed. The appearance of the mucositis and oral candidiasis can be similar; therefore if the assessor is neither trained nor experienced in the diagnosis of these oral lesions, the validity might be affected. Scores of mucositis were not always defined although there was consistency in the number of categories of the indices used, with the lowest indicating no mucositis.

The reporting of outcomes other than mucositis was variable and they were reported more frequently in trials published within the last 5 years than before. The type of outcomes reported has changed to reflect more the characteristics identified as clinically meaningful and important to patients (Bellm 2002). Only interventions to prevent mucositis were included in this review however using a
range of dichotomies for mucositis the findings can be interpreted also as reduction in severity.

Nine of the 21 interventions were found to have some evidence of a benefit (albeit sometimes weak) in preventing or reducing the severity of mucositis. One intervention, folinic acid, was significantly worse than placebo. A summary of the nine potentially effective interventions is given below:

- **Allopurinal** is a xanthine-oxidase inhibitor thought to reduce the mucosal toxicity of chemotherapy drugs. The evidence for its use as a mouthwash is a significant odds ratio of approximately zero (95% confidence interval (CI): 0.0, 0.03) only for a reduction in severe mucositis (Grades 0-2 versus 3) whilst this appears to be a strong finding it is possibly unreliable as it is based on two small trials.

- **Amifostine** is an aminothiol free radical scavenger. It appears to have small benefit in preventing relative risk (RR) = 0.95 (95% CI: 0.91 to 0.99) and reducing the severity of mild mucositis RR = 0.83 (95% CI: 0.72 to 0.97). This is based on the largest body of evidence found in this review, from five trials with 446 participants. The side effects of amifostine were not significantly different to no treatment for survival at 24 months, recurrence at 18 months after cancer treatment, incomplete response to radiotherapy, hypotension and nausea. Delay to radiotherapy was on the borderline of significance with those receiving amifostine less likely to experience a delay RR = 0.44 (95% CI: 0.19 to 1.01). The only significant finding was for vomiting with no patients in the control group compared with 10/182 treated with amifostine experiencing this side effect RR = 5.92 (95% CI: 1.03 to 33.91).

- **Antibiotic as a topical pastille or paste may be beneficial at preventing mucositis RR = 0.87 (95% CI: 0.79 to 0.97) based on two trials with evidence from 198 adults treated for head and neck cancer. The borderline significant result for systemic antibiotics reinforces the potential of antibiotics having some mild benefit.

- **Benzydamine**, an indirect cytoprotectant, was compared to placebo in one trial and was found to be significantly more effective for preventing mucositis RR = 0.67 (95% CI: 0.47 to 0.97). The evidence is weak based on one trial of 36 adult patients with head and neck cancer.

- **GM-CSF and related products** are cytokines which stimulate haemopoiesis and modulate leukocyte functions. Three trials provided evidence that GM-CSF prevents mucositis RR = 0.51 (95% CI: 0.29 to 0.91) and these data were from 249 adults treated for solid tumours. In the absence of evidence for benefit at other levels of mucositis it suggests that GM-CSF may prevent mucositis rather than reduce its severity. Two trials provided useable data for side effects and no difference was found between patients receiving GM-CSF and no treatment control for survival at 24 months, survival at 12 months, relapse within 1 year or nausea. A significant difference was found for local skin reactions with patients receiving GM-CSF more likely to experience a rash RR = 27 (95% CI: 1.71 to 425).

- **Hydrolitic enzymes** have analgesic and anti-inflammatory properties. Two trials provided evidence of moderate benefit at reducing the severity if mucositis rather than preventing it with mucositis 0-1 versus 2+ RR = 0.49 (95% CI: 0.30 to 0.81) and mucositis 0-2 versus 3+ RR = 0.18 (95% CI: 0.06 to 0.53). For both of these comparisons the data were homogeneous, based on 149 adults treated for head and neck cancer in open trials.

- **Ice chips** are thought to act by producing local vasoconstriction therefore limiting the cytotoxic effects of chemotherapy. The evidence is moderate from two trials with 166 patients treated with 5 FU chemotherapy. Significant differences were found at two dichotomies of mucositis, with odds ratios of 0.42 (95% CI: 0.19 to 0.93) and 0.36 (95% CI: 0.15 to 0.89) for absent versus present and 0-1 versus 2+ respectively.

- **Oral care interventions may be beneficial in preventing mucositis is weak, based on a single study of 30 adults treated for head and neck cancer with radiotherapy.**

**Implications for practice**

Several of the interventions were found to have some benefit at preventing or reducing the severity of mucositis associated with cancer treatment. The strength of the evidence was variable and implications for practice include consideration of the fact that benefits may be specific for certain cancer types and treatment.

**Implications for research**

There is a need for well designed and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent. This review has highlighted several interventions for which further research into the benefits and harms should be conducted. There should be continued evaluation of agents for mucositis. Outcome measures of any future trial should address the link between oral and general health including the outcomes relevant to the patient and as a
minimum they should include the reduction of oral pain, the use of opioid analgesics, improvement in oral intake and quality of life, and reduction of hospitalisation duration. Collaboration between medical and dental teams is indicated with a consensus on the choice of objective oral indices for mucositis.

NOTES

The title of the protocol was originally 'Oral care for patients with cancer treated with chemotherapy (excluding head and neck cancer)'.

POTENTIAL CONFLICT OF INTEREST

None known.

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Anderson 1998 [published and unpublished data]

Antonadou 2002 [published data only]

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Brizel 2000 [published data only]

Bubley 1989 [published data only]
Bubley GJ, Chapman B, Chapman SK, Crumpacker CS, Schnipper LE. Effect of acyclovir on radiation- and chemotherapy-induced

Buntzel 1998 [published data only]


Cartee 1999 [published data only]

Carter 1999 [published data only]

Cascinu 1994 [published and unpublished data]

Cengiz 1999 [published data only]

Crawford 1999 [published data only]

Dickson 2000 [published data only]

Dodd 1996 [published and unpublished data]

Dozono 1989 [published data only]

Duenas 1996 [published and unpublished data]

Erlichman 1988 [published data only]


Ferretti 1988 [published and unpublished data]


Ferretti 1990 [published and unpublished data]

Fidler 1996 [published data only]

Foote 1994 [published data only]

Franzen 1995 [published data only]

Gujral 2001 [published data only]

Huang 2000 [published data only]

Jebb 1994 [published and unpublished data]

Katano 1995 [published data only]
Kaul 1999 [published data only]

Koukourakis 2000 [published data only]

Labar 1993 [published data only]

Leborgne 1997 [published data only]

Loprini 1990 [published and unpublished data]

Mahood 1991 [published data only]

Makkonen 1994 [published data only]

Makkonen 2000 [published data only]

Nemunaitis 1995 [published data only]

Niibe 1985 [published data only]

Oberbaum 2001 [published data only]

Okuno 1999 [published data only]

Pfeiffer 1990 [published data only]

Prada 1987 [published data only]

Rahn 1997 [published data only]


Schneider 1999 [published data only]

Shenep 1988 [published and unpublished data]

Shieh 1997 [published data only]

Spijkervet 1989 [published data only]

Symonds 1996 [published data only]
References to studies excluded from this review

Anderson 1998b

Antonadou 1998

Apaydin 1996

Barash 1999

Bensadoun 1999


Chi 1995


Costa 1999

Cowan 1997


Cunningham 1995

Decker-Baumann 1999

Dudjak 1987

Edelman 1998

Epstein 1986

Epstein 1989

Epstein 1992

**Epstein 1994**


**Epstein 1999**


**Epstein 2001**


**Erkisi 1996**


**Etiz 1998**


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**Fahlie 1999**


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**Kenny 1990**


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**Lievens 1998**


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McGaw 1985

Mclroy 1996

Nicholl 1995

Niihe 1985b

Okuno 1997

Okuno 1998

Pfeiffer 1989

Pouli 1999

Prada 1985

Rutkaukas 1993

Samaranayake 1988

Sato 1997

Suc 1999

Vacha 1999

Verdi 1995

Vitello 2000

Wesdorff 1989

Wymenga 1999

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Foncuberta 2001
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Clarkson 2003b

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Elbourne 2002

Gotzsche 1999

Jadad 1998

Kowanko 1998

Lortholary 1997

Meunier 1994

Moher 2001

Stevens 1995

Sunderland 2001

Symonds 1998

Verdi 1993

White 1993

Worthington 2003a

Worthington 2003b

References to other published versions of this review

Clarkson 2003a

* Indicates the major publication for the study
### Characteristics of included studies

<table>
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<tr>
<th>Study</th>
<th>Ahmed 1993</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, parallel group study conducted in USA. Patients, providers and assessors blind. Clear information on withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: return of blood count or resolution of mucositis.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Adults with haematological malignancies prior to BMT after conditioning with etoposide. 12 enrolled and completed.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups, placebo versus propantheline (30 mg every 6 hours during infusion and 12 hours after, for total of 6 doses).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mucositis graded with reference to previous publication. Data presented as number of patients developing mucositis in both groups. Assessment used: day 3. Other reported outcomes: blood counts febrile episodes, survival, tumour response.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>All patients received acyclovir, and nystatin or clotrimazole. Funding source: unclear.</td>
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<td><strong>Allocation concealment</strong></td>
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<tr>
<th>Study</th>
<th>Anderson 1998</th>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, cross-over study conducted in USA. Patients, providers and assessors blind. Clear information on withdrawals. Dentist not involved in study. Drop outs: 46%. Duration 14 days.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Children and adults with solid cancer who have previously had chemotherapy and experienced mucositis. 24 patients eligible and enrolled, 13 completed.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups, glycine control (described as placebo) versus glutamine (4 ml/M² twice daily swish and swallow).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mucositis (patient's description on 0-4 scale). Grade &gt;= 2 painful mucositis which altered food intake. Assessment used: day 14. Other reported outcomes: none.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Funding source: private.</td>
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<th>Study</th>
<th>Antonadou 2002</th>
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<tr>
<td><strong>Methods</strong></td>
<td>Randomised, parallel group study conducted in Greece. Patients, providers and assessors not blind. Clear information on withdrawals: 3/26 control, 2/24 test. Dentist not involved in study. Drop outs: 10%. Duration 3 months.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Adults with head and neck cancer. Radiotherapy total 60-74 Gy 2 Gy fractions 5 days weekly. Chemotherapy carboplatin (90 mg/m2 once per week (no surgery before radiotherapy). 50 patients enrolled, 45 completed.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups, no treatment control versus amifostine 300 mg/m2 15-30 min before radiotherapy for 6-7 weeks.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mucositis assessed weekly EORTC criteria. Assessment used: day 28. Other reported outcomes: dysphagia, xerostomia, treatment interruptions, haematological changes, side effects (nausea, transient hypotension).</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Funding source: unclear.</td>
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### Characteristics of included studies (Continued)

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<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
<th>Funding source</th>
<th>Allocation concealment</th>
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<tr>
<td>Attal 1993</td>
<td>Randomised, parallel group study conducted in France. Patient and providers not blind, unclear whether assessors blind. Clear information on withdrawals: 6/70 control, 6/70 test. Dentist not involved in study. Drop outs: 0%. Duration: day -8 to day +100.</td>
<td>Adults with blood cancer admitted to BMT unit. 140 patients enrolled 6 died in each group, but all were evaluated.</td>
<td>2 groups, no treatment control versus pentoxifylline (oral PTX 1600 mg 1 per day in 4 doses).</td>
<td>Number requiring MSO4 for grade II or higher mucositis (by published criteria). Assessment used: day 100. Other reported outcomes: duration of stay in hospital, renal insufficiency, days morphine, fever, sepsis, 100 day survival.</td>
<td>All patients received fluconazole, acyclovir and ranitidine. Funding source: unclear.</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Borowski 1994</td>
<td>Randomised, parallel group study conducted in France. Patient, providers and assessors not blind. Clear information on withdrawals: 7/82 control, 9/84 test. Dentist involved in study. Drop outs: 7%. Duration: 30 days.</td>
<td>Children and adults with blood cancer and candidates for BMT. 166 eligible and enrolled, 150 completing.</td>
<td>2 groups, limited oral hygiene versus intense oral hygiene (brushing 3 times per day after meals as instructed by dentist).</td>
<td>Moderate or severe mucositis with detailed description of each category. Assessment used: day 30. Other outcomes: plaque, fever, sepsis.</td>
<td>Chlorhexidine mouthrinse used at least 5 times daily by both groups. Funding source: unclear.</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Bourhis 2000</td>
<td>Randomised, parallel group study conducted in France. Patients and providers not blind, unclear whether assessors blind. Unclear information on withdrawals: 1 died and 1 refused, unclear which group. Dentist not involved in study. Drop outs: 8%. Duration: unclear.</td>
<td>Adults with head and neck cancer, stage IV not amenable to conventional radiosurgical treatment. Karnofsky performance &gt; 60. Radiotherapy 64 Gy in 22-23 days. 26 patients enrolled, 24 were evaluated.</td>
<td>2 groups, no treatment control versus amifostine (subcutaneous infusion 150 mg/m² amifostine administered IV twice daily 15-30 mins prior to each radiotherapy session).</td>
<td>Max WHO grade (I to IV). Assessment used: day 23. Other reported outcomes: duration of feeding tube, vomiting, liver function, erythema (tolerance of amifostine). Duration of feeding tube.</td>
<td>RTOG index also given with mean duration of at least grade 3 mucositis. Funding source: pharmaceutical.</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Brizel 2000</td>
<td>Randomised, parallel group study conducted as multicentre USA, Germany and France. Patients, providers and assessors blind. Clear information about withdrawals: none. Drop outs: 0%. Duration: 1 year.</td>
<td></td>
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<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Participants</th>
<th>Adults with head and neck cancer. Newly diagnosed squamous cell radiation more than or equal to 70% both parotid glands more than or equal to 40 Gy - daily 2 Gy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>2 groups, no treatment control versus amifostine 200 mg/m² daily 15-20 minutes prior to radiation.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mucositis assessed weekly by physician. Radiation Therapy Oncology Group Scoring systems. Assessment used: day 90. Other reported outcomes: nausea, vomiting, xerostomia, saliva production, survival, local disease control.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding Source: pharmaceutical.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Bubley 1989</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adults with head and neck cancer. Prior positive titre to Herpes Simplex.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, placebo versus acyclovir 200 mg tablets 12 hourly.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mucositis assessed by nurse. Assessment used: unclear. Other reported outcomes: herpes simplex virus.</td>
</tr>
<tr>
<td>Notes</td>
<td>Data presented separately for patients receiving chemo and radiotherapy. Funding source: pharmaceutical.</td>
</tr>
<tr>
<td>Allocation concealment</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Buntzel 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adults with head and neck cancer, hospitalised with stage III-IV tumour, no evidence of systemic infection, liver or renal impairment, tumour resected or excised before adjuvant radiotherapy. 28 patients enrolled, 28 were evaluated.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, radiotherapy with or without amfostine (15 min infusion 500 mg preceded by antiemetic regime of 12 mg dexamethasone and 8 mg ondansetron).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>WHO mucositis grades 3/4. Assesment used: day 42. Other reported outcomes: xerostomia, dysphagia, loss of taste, dermatitis, haematological side effects.</td>
</tr>
<tr>
<td>Notes</td>
<td>More data presented but included extra 11 patients in amifostine group who were not entered into study. Funding source: pharmaceutical.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>B</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Cartee 1995</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in USA. Patient, provider and assessor blind. Unclear information on withdrawals: 5 withdrew, unclear from which groups. Dentist involved in study. Drop outs: 10%. Duration: 21 days.</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults with breast cancer stage IV, with combination of chemotherapy including 5-FU, Adriamycin &amp; methotrexate. First cycle of chemotherapy. 50 patients were enrolled and 45 were evaluated.</td>
</tr>
<tr>
<td>Interventions</td>
<td>5 groups, 0.1% albumin (described as placebo, dose 0), GM-CSF (molgramostim, range of doses, 0.01, 0.10, 1.00, 10.00 mcg/ml. Mouthwash solutions administered 4 times daily starting 24 hours after chemotherapy initiation). continuing until end of cycle.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mucositis (CALGB GRADE &gt;= 3). Assessment used: day 15. Other reported outcomes: WBC, plasma GM-CSF.</td>
</tr>
<tr>
<td>Notes</td>
<td>Doses 0.01, 0.10, 1.00, 10.00 were combined and compared with dose 0 (control).</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

**Allocation concealment A**

<table>
<thead>
<tr>
<th>Study</th>
<th>Carter 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in USA. Patient, provider and assessor blind. Clear information on withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: up to 4 months postradiotherapy.</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults with head and neck cancer receiving curative intent radiotherapy, Karnofsky performance &gt; 60. 102 patients enrolled and 102 completed.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, placebo versus sucralfate (added as suspension of 1 gm sucralfate/15 ml solution) swish 2 mins and swallow 4 times per day.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>RTOG graded mucositis. Assessment used: maximum during treatment at 60 Gy. Other reported outcomes: pain, need for placement of feeding tube, use of narcotics, need for intravenous fluids, diet, need for treatment break. All assessed weekly.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding source: government.</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Cascinu 1994</th>
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</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adults with solid cancer (GI &amp; prostate). Chemotherapy: 5-FU fluorouracil. First course of chemotherapy. 84 patients eligible, enrolled and completed.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, control (no treatment) versus ice chips (cryotherapy, 5 mins before 5-FU for 30 mins after). Checked every week and judgement on mucositis performed on day of next chemotherapy course.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mucositis (Global assessment of physician's and patient's description on 0-4 scale). Assessment used: unclear.</td>
</tr>
<tr>
<td>Notes</td>
<td>Statistical handling of data incorrect as all cycles included but used data from first cycle. Funding source: unclear.</td>
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<thead>
<tr>
<th>Study</th>
<th>Cengiz 1999</th>
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</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adults with head and neck cancer. 28 patients enrolled and completed.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, placebo versus sucralfate (6 g sucralfate suspension mouthwash 4 doses orally before meals and bedtime).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>RTOG mucositis (0-IV). Topical and systemic analgesic use, weight loss, dry mouth. Assessment used: day 42. Other reported outcomes: pain, difficulty eating, constipation, analgesics, dry mouth.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding source: unclear.</td>
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</tbody>
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<thead>
<tr>
<th>Study</th>
<th>Crawford 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in USA. Patient blind, unclear whether assessor and provider was. Unclear information on withdrawals (previously described): 6/110 placebo, 6/101 test. Dentist not involved in study. Drop outs: 9%. Duration: from day 4 to day 17 of cycle.</td>
</tr>
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</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Dickson 2000</th>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, parallel group study conducted in USA. Patient not blind (c), assessor blind and unclear whether provider was. Clear information on withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: first day of treatment until discharge or max 28 days after transplant.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Adults receiving bone marrow transplant (BMT). 58 enrolled and evaluated with haematological and solid cancer.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups, sugar water (placebo) versus glutamine (30 g in 10 g doses mixed with food or liquid chosen by patient).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Stamford University Hospital BMT toxicity scale for mucositis scale 0-4. Reported as grade 2+. Parenteral nutrition with TPN. Assessment used: day 28. Other reported outcomes: length of hospital stay. Days in total, parenteral nutrition, diarrhoea, toxicity.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Funding source: pharmaceutical supply product.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
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<thead>
<tr>
<th>Study</th>
<th>Dodd 1996</th>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, parallel group study conducted in USA. Patient not blind (c), providers and examiners were blind. Clear information on withdrawals: none. Dentist involved in study. Drop outs: 0%. Duration: up to 3 months.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Adults with solid cancer receiving chemotherapy. Followed for 3 cycles of chemotherapy. 303 eligible, 227 enrolled and evaluated.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups: water control (described as placebo) versus chlorhexidine mouthrinse (0.12%, 20 ml, 2 times per day).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Oral Assessment Guide (OAG) 0-24, scores over 10 were considered to be oral mucositis. Maximum of 3 months. Assessment used: day 90. Other reported outcomes: cost.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Severity of mucositis at onset measured. Intent to treat analysis. Funding source: government.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Dozono 1989</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, cross-over study conducted in Japan. Patients and providers were not blind, it is unclear if assessor was. Clear information on withdrawals: none. Unclear if dentist was involved. Drop outs: 0%. Duration: unclear.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Adults with solid cancer receiving chemotherapy. 15 patients enrolled and completed both periods.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups: no treatment control versus allopurinol mouthwash (carboxymethylcellulose (CMC-Na) 5 g and allopurinol 500 mg, water to 500 ml solution).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Japan Society for Cancer Therapy criteria for stomatitis 0-4 scale.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Funding source: unclear.</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

#### Allocation concealment A

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomised, parallel group study conducted in Mexico. Patients, providers and assessors were blind. Clear information on withdrawals: none. Unclear if dentist was involved in study. Drop outs: 0%. Duration: -4 to day 16.</td>
<td>Adults with mixed cancer undergoing peripheral stem cell transplant, receiving high dose (ifosfamide, carboplatin, etoposide). 15 patients enrolled (16 course of chemotherapy).</td>
<td>2 groups, placebo versus misoprostol (racemic prostaglandin E1 analogue) 250 ug 3 times per day.</td>
<td>WHO mucositis grades 0-4, candidiasis, days in hospital with range. Assessment used: day 16. Other reported outcomes: diarrhea, fever, days in hospital, duration of antibiotics.</td>
<td>All patients received fluconazole prophylaxis. Also received ranitidine, ketoconazole &amp; ciprofloxacin. Severity of mucositis also given but no SD. Study stopped prematurely due to a significant finding at an interim analysis, favouring the placebo. Funding source: government, pharmaceutical.</td>
</tr>
</tbody>
</table>

#### Allocation concealment A

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomised, parallel group study conducted in Canada. Patients and providers not blind, unclear whether assessor blind. Unclear information on withdrawals. Dentist not involved in study. Drop outs: 4%. Duration: unclear.</td>
<td>Adults with solid cancer - recurrent colorectal metastatic. Chemotherapy 5 FU.</td>
<td>2 groups, no treatment control versus folic acid 200 mg/m2/d 5 consecutive days before 5 FU. 206 eligible, 130 enrolled, 165 completed.</td>
<td>mucositis (clinical 0-3 scale). Assessment used: day 28. Other reported outcomes: GI toxicity grades.</td>
<td>Funding source: pharmaceutical.</td>
</tr>
</tbody>
</table>

#### Allocation concealment B

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomised, parallel group study conducted in USA. Patient, providers and assessors were blind. Unclear information on withdrawals: 1/28 control, 4/28 test. Dentist involved in study. Drop outs: 10%. Duration: up to 90 days.</td>
<td>Children and adults (1-51 years) with mixed blood haematological and solid cancers receiving BMT. 56 patients enrolled and 51 completed. Data used n=41.</td>
<td>2 groups, placebo versus chlorhexidine gluconate mouthrinse (15 cc 0.12%, 3 times per day for 30s).</td>
<td>mucositis (clinical scale 0-3, but then dichotomised and measured at 7, 14, 25, 33, 60 &amp; 90 days). Assessment used: day 33. Other reported outcomes: gross candida (clinical appearance + swab culture or KOH preparation), oral streptococus, yeast, gram -ve bacilli, death, morphine use.</td>
<td>Candidemia (persistent candidiasis) also recorded, with 3 deaths due to candida in the control group. Mean mucositis scores given graphically with bars for SE. Given oral nystatin suspension 15 ml 4 times daily or clotrimazole troches . Supplemental nystatin soaks or popsicles were used liberally. Funding source: pharmaceutical.</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Ferretti 1990</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, parallel group study conducted in USA. Patient, providers and assessors were blind. Unclear information on withdrawals: 18/46 control, 15/46 test. Dentist involved in study. Drop outs: 36%. Duration: 28 days.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Children and adults (1-70 years) with mixed blood and solid cancer. High dose chemotherapy or head and neck radiation (data separate). 92 enrolled, 59 completed.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups, placebo versus chlorhexidine 0.12% ml 3 times/day.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mucositis (scale where 0 = no ulceration) Assessment used: day 28+. Other reported outcomes: oral micr-strep, yeast, gram-ve bacilli. Systematic infection measured at day 7, 14, 21, 28.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Mucositis severity given with no s.d. Both groups had some mucositis at baseline. Funding source: pharmaceutical.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
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<thead>
<tr>
<th>Study</th>
<th>Fidler 1996</th>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, parallel group study conducted in USA. Patient, providers and assessors were blind. Unclear information on withdrawals: 1/165 total. Dentist not involved in study. Drop outs: 1%. Duration: 14 days.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Adults, cancer type not given. Chemotherapy: first course 5-FU based. 165 enrolled, 164 clinical evaluation, 135 patient evaluation.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups, placebo versus camomile (30 drops in 100 ml water, 3 times per day).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mucositis (physician and patient scales 0-4). Score judged historically 4-5 weeks after chemotherapy cycle initiation. Additionally patient form filled out on daily basis for first 3 weeks after first day of chemotherapy. Assessment used: day 21. Other reported outcomes: toxicity.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Mean daily mucositis scores shown graphically but no s.d. All patients used ice chips 5 mins before chemotherapy and for 30 minutes in total. Patient's mucositis scores used. Funding source: government.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Foote 1994</th>
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</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, parallel group study conducted in USA and Canada. Patient, providers and assessors were blind. Clear information on withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration: 14 days.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Adults with head and neck cancer. 52 patients were eligible, enrolled and evaluated.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups, placebo versus chlorhexidine (15 ml 4 times per day for 130s).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mucositis scale 0-4 by patient and clinician at weekly intervals. Assessment used: day unclear.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Funding source: pharmaceutical and government.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
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<thead>
<tr>
<th>Study</th>
<th>Franzen 1995</th>
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</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, parallel group study conducted in Sweden. Patient, providers and assessors were blind. Statistician blind. Unclear information on withdrawals: 2/50 total. Unclear if dentist involved in study. Drop outs: 10%. Duration: -2 to 14 weeks.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Adults with head and neck cancer. 50 patients were enrolled and 48 evaluated.</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Gujral 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in India. Patients, providers and assessors nor blind. Unclear information about withdrawals. Dentist no involved in study. Drop outs: 1%. Duration: 6 months.</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults with head and neck cancer. T3 and T4 squamous cell cancer, 100 enrolled, 99 evaluated.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, no treatment versus hydrolytic enzymes, papain 100 mg, trypsine 40 mg and chymotrypsine 40 mg. 3 tablets 3 times a day - 3 until + 5.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>RTOG/EORTE scoring. Assessment used: day 54. Other reported outcomes: dysphagia, dermatitis.</td>
</tr>
<tr>
<td>Notes</td>
<td>No oral care except toothbrushing. Funding source: pharmaceutical.</td>
</tr>
<tr>
<td>Allocation concealment</td>
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<thead>
<tr>
<th>Study</th>
<th>Huang 2000</th>
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<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in Taiwan. Unclear whether patient, providers and assessors were blind. Clear information about withdrawals (c): none. Dentist not involved in study. Drop outs: 0%. Duration: beginning of radiation treatment until 25 factions (5 weeks).</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults with head and neck cancer. 17 patients were evaluated.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, placebo (30 ml saline) versus glutamine (2 g in 30 ml saline, swish 30 ml 3 mins exporate).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinicians assessed subjective mucositis on 0-4 scale and objective RTOG/EORTC 0-4 scale. WHO step of analgesic drugs. Assessment used: day unclear.</td>
</tr>
<tr>
<td>Notes</td>
<td>Subjective mucositis scale used. Funding source: none.</td>
</tr>
<tr>
<td>Allocation concealment</td>
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<thead>
<tr>
<th>Study</th>
<th>Jebb 1994</th>
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<tbody>
<tr>
<td>Methods</td>
<td>Randomised, cross-over study conducted in UK. Patient, providers and assessors were blind. Unclear information about withdrawals: 11/28 in total. Dentist not involved in study. Drop outs: 39%. Duration: (1st part) 8 days.</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults with gastrointestinal cancer undergoing 5-FU &amp; folic acid daily for 5 days and repeated 4 weeks from start. 28 patients enrolled and 17 completed 2 cycles.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, glucose polymer (Polycal) (described as placebo) versus glutamine (16 gm daily divided into 4 equal doses and dissolved in 150 ml water before consumption).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>WHO mucositis score, mouth comfort, ease of eating. Assessment used: day 8.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding source: none.</td>
</tr>
<tr>
<td>Allocation concealment</td>
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<tr>
<th>Study</th>
<th>Katano 1995</th>
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<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in Japan. Patients, providers and assessors were not blind (c). Clear information about withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: administration ceased when leukocyte exceeded 8,000/mm³.</td>
</tr>
</tbody>
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Interventions for preventing oral mucositis for patients with cancer receiving treatment (Review)  
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### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Kaul 1999</th>
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<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in India. Patient, provider and assessor not blind. Unclear information about withdrawals. Dentist not involved in study. Drop outs: 3%. Duration: 6-7 weeks.</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults with head and neck cancer radiotherapy 50-60 Gy/5-6 weeks. 50 patients enrolled.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, no treatment control versus amifostine 500 mg daily before RT.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mucositis. Assessment used: day 28. Other reported outcomes: xerostomia, skin changes, dysphagia, hospitalisation.</td>
</tr>
<tr>
<td>Notes</td>
<td>Patients selected from other types of cancer because mucositis data available. Funding source: government &amp; pharmaceutical.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Labar 1993</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in Croatia. Patients and assessors blind but unclear if providers were. Clear information about withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: +7 to day +21.</td>
</tr>
<tr>
<td>Participants</td>
<td>Children and adults (5-43 years) with blood and solid cancers, undergoing BMT. 60 patients eligible, enrolled and evaluated.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, placebo versus prostaglandin E2 (0.5 mg 3 times per day).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical and culture fungal measurement. Mucositis (WHO scale for 0-II vs III+, and 0 vs 1+). Severity over -7 to +35 days. Severity of mucositis also measured but no s.d. given. Assessment used: day 35. Other reported outcomes: HSV infection, microbiology, vomiting, diarrhoea, fever, death, GVHD (c).</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding source: none.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Leborgne 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in Uruguay (c). Patient, provider and assessor blind. Unclear information about withdrawals. Dentist not involved in study. Drop out: 4%. Duration 90 days.</td>
</tr>
</tbody>
</table>
Characteristics of included studies *(Continued)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Loprinzi 1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised cross-over trial conducted in USA. Patients, providers and assessors were blind. Clear information on withdrawals: none. Dentist was not involved. Drop outs: 0%. Duration: 5 days.</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults with colorectal cancer receiving first 5 day course of 5-FU. 77 patients enrolled, and completed 1st period, only 20 completed 2nd period.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, placebo versus allopurinol mouthrinse 1 mg/ml made from 450 mg + 150 ml cologel (450 mg/5 mg methylcellulose with 5% alcohol) +450 ml flavouring agent. 20 ml used for 30s immediately after treatment then at 1, 2, 3 hours).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mucositis (physician and patient scales 0-4). Assessed used: day 30.</td>
</tr>
<tr>
<td>Notes</td>
<td>Data cross-tabulated in a form suitable for meta-analysis provided by authors. Funding source: none.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>A</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Mahood 1991</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, cross-over study conducted in USA. Patients, providers and assessors not blind. Unclear information on withdrawals: 2/45 control, 0/50 treatment in first cycle. Dentists not involved in study. Drop outs 2%. Duration from 5 mins before 5-FU and for 30 mins after.</td>
</tr>
<tr>
<td>Participants</td>
<td>Unclear age group and cancer type. Chemotherapy first 5 day course of 5-FU. 95 patients eligible and enrolled and 93 completed first cycle, however, only 82 patients assessed mucositis.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, no treatment control versus ice chips (cryotherapy) placed in the mouth 5 mins before each dose of 5 FU and replenished over 30 mins.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mucositis (physician &amp; patients scales 0-4) and historical 1 month after treatment. Assessment used: day 28.</td>
</tr>
<tr>
<td>Notes</td>
<td>Data cross-tabulated in a form suitable for meta-analysis provided by authors. Funding source: government.</td>
</tr>
<tr>
<td>Allocation concealment</td>
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<thead>
<tr>
<th>Study</th>
<th>Makkonen 1994</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in Finland. Patients blind but unclear if providers and assessors were. Clear information about withdrawals: none mentioned. Dentist involved in study. Drop outs: 0%. Duration: during therapy (9 wks).</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults with head and neck cancer. 40 patients eligible, enrolled and evaluated.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, placebo versus sucralfate (suspension 1 g 6 times per day orally, patients mix granules with 100 ml water rinse for 1 min then swallow). Rinsed throughout radiotherapy, dose 45-73 Gy.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mucositis on scale 0-2 (0 = no mucositis, 1 = moderate, 2 = severe), at 9 weekly evaluation visits. Assessment used: day 28. Other reported outcomes: salivary lactoferrin, salivary albumin, amount of anesthetic mouthwash, radiotherapy interrupted, toxicity.</td>
</tr>
<tr>
<td>Notes</td>
<td>Visit at week 4 taken. Antifungal agents given to 29 patients during study. Funding source: government.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>A</td>
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</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Makkonen 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, parallel group study conducted in Finland. Patients, providers and assessors not blind. Clear information about withdrawals: none. Dentist involved in study. Drop outs:0%. Duration: during therapy (9 wks).</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Adults with head and neck cancer. 40 patients eligible, enrolled and evaluated.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups, no treatment control versus GM-CSF (150 to 300 ug given subcutaneously daily until last day of irradiation. Dose depends on body weight).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mucositis on scale 0-2 (0 = no mucositis, 1 = moderate, 2 = severe). Assessment used: day 28. Other reported outcomes: oral pain on scale 1-4, and patient VAS scale for pain. Evaluated weekly during treatment then 1 and 6 months after therapy, use of analgesic, weight loss, toxicity, survival.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>All patients used sucralfate suspension 1 g 6 times daily. Funding source: pharmaceutical.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
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<thead>
<tr>
<th>Study</th>
<th>Nemunaitis 1995</th>
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</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>Adults with mixed cancer receiving BMT, chemotherapy cyclosporine &amp; prednisolone. 109 patients enrolled, 109 completed.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups, placebo versus RhGM-CSF (human granulocyte macrophage colony stimulating factor) 250 μg/m2/day IV day 0-20.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mucositis scored by nurse 3 grades. (Categorised according to WHO criteria for analysis). Assessment used: day 28. Other reported outcomes: infection, anorexia, diarrhea, hypertension, stomatitis.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Funding source: pharmaceutical.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
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<tr>
<th>Study</th>
<th>Niibe 1985</th>
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</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>Adults with head and neck cancer. 47 patients enrolled and 37 completed.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups, placebo versus amifostine (200 mg per day).</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mucositis measured at &gt;= 2 on scale similar to WHO scale. Assessment used: day unclear.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Funding source: unclear.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
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<thead>
<tr>
<th>Study</th>
<th>Oberbaum 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, parallel group study conducted in Israel. Patients, providers and assessors blind. Clear information about withdrawals: 1/16 control, 1/16 test. Drop outs: 6%. Duration: unclear.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Children and adults with mixed cancer receiving a BMT. 32 consecutive patients enrolled, 30 completed.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>2 groups, placebo versus traumeel (homeopathic) rinse vigorously 30 sec before swallowing 5/day for a minimum 14 days.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mucositis WHO scale evaluated every 2 days. Assessment used: day 7.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>All patients 2 daily chlorhexidine oral amphotericin B.</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

Funding source: pharmaceutical and possibly charity.

<table>
<thead>
<tr>
<th>Allocation concealment</th>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Okuno 1999</td>
<td>Randomised, parallel group study conducted in USA. Patients, providers and assessors blind. Clear information about withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: up to 5 weeks after intral chemotherapy.</td>
<td>Adults with cancer (type unclear). 134 eligible, enrolled and evaluated, but patient assessment only completed by 124 patients.</td>
<td>2 groups, placebo versus glutamine (4 g twice a day, swish for 10 s then swallow).</td>
<td>Maximum severity of mucositis over 14 days using 0-4 scale, both physician and patient assessment. Other reported outcomes: toxicity (no detail). Assessment used: day 14.</td>
<td>All patients used ice chips 5 minutes before 5 FU for 30 minutes. Funding source: government.</td>
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<td>Pfeiffer 1990</td>
<td>Randomised, cross-over study conducted in Denmark. Patients, providers and assessors blind. Unclear information about withdrawals. Dentist not involved in study. Drop outs: 43%. Duration: 14 days.</td>
<td>Adults with mixed cancer (including head and neck). 40 patients enrolled, 23 evaluable.</td>
<td>2 groups, placebo versus sulcralfate (1 g 15 ml suspension, swish for 2 min then spit out or swallow).</td>
<td>Ulceration or not. Assessment used: day 14. Other reported outcomes: pain, problems eating.</td>
<td>Funding source: pharmaceutical support for product.</td>
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<td></td>
<td>Prada 1987</td>
<td>Randomised, parallel group study conducted in Italy. Patients, providers and assessors blind. Unclear information about withdrawals. Dentist not involved in study. Drop outs 10%. Duration: 10 days.</td>
<td>Adults with head and neck cancer. 40 patients eligible and enrolled, 36 evaluated.</td>
<td>2 groups, placebo versus benzydamine (120 ml solution of 0.15% benzydamine, 15 ml mouthwash for 5 mins every 3 hours up to max of 6 times daily.</td>
<td>Physician evaluation of mucositis on 0 (absent) to 3 (intense or remarkable) scale every day for 10 days. Assessment used: day 10. Other reported outcomes: global clinical symptomatology, burning, chewing pain, dysphasia and odynophasia assessed.</td>
<td>Funding source: none.</td>
</tr>
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<td></td>
<td>Rahn 1997</td>
<td>Randomised, parallel group study conducted in Germany. Patients and providers not blind, assessors were blind (c). Clear information about withdrawals: none. Dentist involved in study. Drop outs: 0%. Duration: until one week after end of radiotherapy.</td>
<td>Adults with head and neck cancer. 40 patients eligible, enrolled. 2 died but all 40 were evaluated</td>
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</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schneider 1999</td>
<td>Randomised, parallel group study conducted in USA. Patients, providers and assessors blind. Clear information about withdrawals: none. Dentist involved in study. Drop outs: 0%. Duration:</td>
<td>Adults with head and neck cancer. 14 patients enrolled and evaluated.</td>
<td>2 groups, placebo versus filgrastim (subcutaneous injections daily throughout treatment titrated to keep neutrophil count between $10^7$ and $30\times10^9/l$).</td>
<td>WHO mucositis 0-4 scale, and Hickey mucositis scores. Proportion of patients greater than WHO mucositis grade 3 presented. Assessment used: week 10.</td>
<td>All patients had oral hygiene instruction. Funding source: pharmaceutical.</td>
</tr>
<tr>
<td>Shenep 1988</td>
<td>Randomised, parallel group study conducted in USA. Patients, providers and assessors blind. Clear information about withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: 50 days.</td>
<td>Children with leukaemia. Chemotherapy- remission induction multiagent ANLL-83. 48 patients enrolled and evaluated.</td>
<td>2 groups, placebo versus sucralfate (0.75 mg/kg daily, suspension swished every 6 hours).</td>
<td>Mucositis (clinical and patients scales given, 0-4), gram-ve, gram+ve, fungal, all organisms. Assessment used: day 50. Other reported outcomes: gastroenteritis, gingival bleeding, nutrition, fever, infection, rash.</td>
<td>Clinician’s mucositis score used. Funding source: government.</td>
</tr>
<tr>
<td>Shieh 1997</td>
<td>Randomised, parallel group study conducted in China. Patients not blind, unclear whether providers and assessors blind (c). Clear information about withdrawals: none. Dentist involved in study. Drop outs: 0%. Duration: 5 weeks.</td>
<td>Adults with head and neck cancer. 30 patients enrolled and evaluated.</td>
<td>3 groups (oral care protocols), control given no instructions, E1 given protocol to follow 1 day before radiotherapy, E2 given protocol to follow 1 week before radiotherapy. Oral care protocol included instructions on how to brush teeth.</td>
<td>Stomatitis free survival (graph). Also means and standard deviations of oral assessment guide (OAG) index, which includes multiple factors including voice and teeth. Assessment used: day 28.</td>
<td>Funding source: government.</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spijkervet 1989</td>
<td>Randomised, parallel group study conducted in the Netherlands. Patients, providers and assessors blind. Clear information about withdrawals: none. Dentist involved in study. Drop outs: 0%. Duration: 5 weeks.</td>
<td>Adults with head and neck cancer. 30 patients eligible, enrolled and evaluated.</td>
<td>2 groups, placebo versus chlorhexidine spray/rinse (0.1% chlorhexidine 100 ml per day (spray 50 ml) rinsing 3 times with 15 ml).</td>
<td>Semiquantitative scoring of mucositis in ‘described elsewhere’. Assessed thrice weekly until end of treatment (at least 50 Gy). Assessment used: day 35.</td>
<td>Used data from text: 24 patients showed the most severe stage of pseudomembrane formation (12 in placebo and 12 in test). During radiotherapy daily cleaning of teeth by hygienist. Funding source: government.</td>
<td>B</td>
</tr>
<tr>
<td>Symonds 1996</td>
<td>Randomised, parallel group study conducted in Scotland. Patients, providers and assessors blind. Clear information about withdrawals: 30/139 control, 24/136 test. Dentist not involved in study. Drop outs: 20%. Duration: until radiation reaction settled, 8 weeks.</td>
<td>Adults with head and neck cancer. 275 patients enrolled and 221 evaluated.</td>
<td>2 groups, placebo versus antibiotic pastille (polymyxin E 2 mg, tobramycin 1.8 mg and amphotericin B 10 mg, 4 times daily from start of radiotherapy).</td>
<td>Physician assessment of mucositis (none, patchy confluent). Assessment used: day 56. Other reported outcomes: patients asked about pain on swallowing and dysphagia, weight loss and compliance.</td>
<td>Funding source: none.</td>
<td>B</td>
</tr>
<tr>
<td>Van der Leslie 2001</td>
<td>Randomised, parallel group study conducted in Holland. Patients, providers and assessors blind. Clear information about withdrawals: none. Dentist involved in study. Drop out: 0%. Duration: until neutrophil recovery.</td>
<td>Adults with mixed cancer receiving BMT or cell stem. 39 patients eligible, 36 enrolled and evaluated.</td>
<td>2 groups, placebo versus GM-CSF (300 ug of GM-CSF daily dose in 2% methylcellulose gel, 5 ml gel twice daily, keep in oral cavity as long as possible then swallow).</td>
<td>WHO mucositis scale 0-4. Assessment used: day 14. Other reported outcomes: VAS mucositis pain, OAS mucositis, required morphine or not, fever, infection treated with antibiotics, duration of neutropenia, days in hospital.</td>
<td>All rinsed with 0.9% saline and in case of inflammation 0.12% chlorhexidine 6 times daily. Funding source: university, pharmaceutical for intervention.</td>
<td>A</td>
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</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Wijers 2001</th>
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</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in the Netherlands. Patients were not blind, unclear if providers and assessors were. Unclear information about withdrawals. Dentist involved in study. Drop outs: 32%. Duration: 3 weeks after radiation.</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults with head and neck cancer. 114 patients enrolled, 37 refused to continue, 77 completed.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups, placebo versus PTA paste containing antibiotics, polymyxin E, tobramycin, amphotericin.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mucositis scored weekly, 5 point scale, Van der Schneren system. Assessment used: day 28 min. Other reported outcomes: pain, microflora.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding source: unclear.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Yuen 2001</th>
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</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, parallel group study conducted in Hong Kong. Patients, providers and assessors not blind. Clear information on withdrawals: none. Dentist no involved in study. Drop outs: 0%. Duration: 60 days after BMT.</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults with mixed cancer receiving BMT, 70 enrolled, 70 evaluated.</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 groups no treatment versus Clarithromycin oral 500 mg twice daily or IV 500 mg 12 hourly. Start day -7.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mucositis scoring system not clear. Grade 2 data used. Assessment used: unclear. Other reported outcomes: toxicity (rash, diarrhoea, liver function), infection, duration of fever, neutropenic fever, use of antibiotics, parenteral nutrition, growth factors.</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding Source: none.</td>
</tr>
</tbody>
</table>

### Characteristics of excluded studies

- **Anderson 1998b** Data not in suitable form, need number per group for self reported mouth sores for Fig 3 otherwise cannot use data. (Glutamine versus placebo).
- **Antonadou 1998** Abstract, insufficient information. (Radiotherapy with or without GM-CSF).
- **Apaydin 1996** Data not in suitable form. Unclear how mucositis assessed and means (SD) given. (Benzydamine versus no treatment).
- **Barasch 1995** Data not in suitable form. Mucositis presented as mean area (SD). (He-Ne Laser versus no treatment).
- **Bensadoun 1999** Data not in suitable form. Mean (SD) of mucositis grade intensity per week. (He-Ne Laser versus no treatment).
- **Chi 1995** Data not in suitable form. Written to authors requesting cross-tabulated data. (GM-CSF versus no treatment).
- **Costa 1999** Abstract, insufficient information. (Chlorhexidine versus no treatment).
## Characteristics of excluded studies (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowen</td>
<td>1997</td>
<td>Data in inappropriate form. Daily mucositis index ranging from 0-48 used, with means (SD) presented. (He-Ne Laser versus no treatment).</td>
</tr>
<tr>
<td>Cunningham</td>
<td>1995</td>
<td>Investigating new cancer treatment, Tomudex, with oral mucositis as one of the minor side effects.</td>
</tr>
<tr>
<td>Decker-Baumann</td>
<td>1999</td>
<td>Unsuitable treatment outcome for review. (Parental glutamine versus no treatment).</td>
</tr>
<tr>
<td>Dudjak</td>
<td>1987</td>
<td>Data not in suitable form. Mean (SD) of mouth and comfort scores. (Two oral care protocols).</td>
</tr>
<tr>
<td>Edelman</td>
<td>1998</td>
<td>Not RCT. (Cryotherapy).</td>
</tr>
<tr>
<td>Epstein</td>
<td>1986</td>
<td>Mucositis not presented in a useable form, however VAS pain scores presented. (Benzydamine versus placebo).</td>
</tr>
<tr>
<td>Epstein</td>
<td>1989</td>
<td>Data not in suitable form. Mean (SD) for size and area of ulceration presented. (Benzydamine versus placebo).</td>
</tr>
<tr>
<td>Epstein</td>
<td>1992</td>
<td>Data not in suitable form. Mean (SD) for size and area of ulceration presented. (Three groups: chlorhexidine rinse, nystatin suspension and saline solution).</td>
</tr>
<tr>
<td>Epstein</td>
<td>1994</td>
<td>Data not in suitable form. Mean (SD) mucositis scores presented. (Sucralfate versus placebo).</td>
</tr>
<tr>
<td>Epstein</td>
<td>1999</td>
<td>Abstract, insufficient information. (Benzydamine versus placebo).</td>
</tr>
<tr>
<td>Epstein</td>
<td>2001</td>
<td>Excluded due to mucositis data presented as area under the curve. (Benzydamine versus placebo).</td>
</tr>
<tr>
<td>Erkisi</td>
<td>1996</td>
<td>Design fault-intervention confounded by radiotherapy. (G-CSF versus no treatment).</td>
</tr>
<tr>
<td>Etiz</td>
<td>1998</td>
<td>Abstract, insufficient information. (Sucralfate versus placebo).</td>
</tr>
<tr>
<td>Etiz</td>
<td>2000</td>
<td>Data not in suitable form. Median oral mucositis scores and pain scores presented. (Sucralfate versus placebo).</td>
</tr>
<tr>
<td>Fahlke</td>
<td>1999</td>
<td>Not RCT. (Amifostine).</td>
</tr>
<tr>
<td>Falcone</td>
<td>2001</td>
<td>Comparing different radiotherapy regimens.</td>
</tr>
<tr>
<td>Grotz</td>
<td>2001</td>
<td>Data not in suitable form. Total RTOG scores mean (SD) presented. (Comarin/troxerutine versus placebo).</td>
</tr>
<tr>
<td>Hanson</td>
<td>1997</td>
<td>Data not in suitable form. Mucositis mean (SD) graphically presented. (Prostaglandin versus placebo).</td>
</tr>
<tr>
<td>Harris</td>
<td>1995</td>
<td>Abstract, insufficient information. (Folinic acid mouthwash versus placebo).</td>
</tr>
<tr>
<td>Hickey</td>
<td>1982</td>
<td>Problems with data. 21 patients in total, unclear how many patients per group, but data presented as 67 courses of chemotherapy. (Oral hygiene protocols).</td>
</tr>
<tr>
<td>Jebb</td>
<td>1995</td>
<td>Data not in suitable form. Mean (SD) mucositis scores presented. (Glutamine versus placebo).</td>
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<tr>
<td>Karthaus</td>
<td>1998</td>
<td>Problems with the data. 8 patients, 32 chemo cycles and results presented assuming independent. (G-CSF versus placebo).</td>
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<td>Kenny</td>
<td>1990</td>
<td>Data not in suitable form. Oral assessment guide mean (SD) presented. (Two oral care protocols).</td>
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<tr>
<td>Lievens</td>
<td>1998</td>
<td>Data not in suitable form. Mean (SD) mucositis scores presented graphically. (Sucralfate versus placebo).</td>
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<tr>
<td>Lopez</td>
<td>1994</td>
<td>Data not in suitable form. Number of days with mucositis presented. (Vitamin E versus placebo).</td>
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<tr>
<td>Marcial</td>
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<td>Abstract, insufficient information. It states it is an RCT but mentions historical control group. (Low energy laser versus no treatment).</td>
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<tr>
<td>McGaw</td>
<td>1985</td>
<td>Data not in suitable form. Did not give the numbers in the 2 study groups and data presented as mean (SD) mucositis index. (Chlorhexidine versus placebo).</td>
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<td>McIlroy</td>
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<td>Data not in suitable form. Qualitative assessment with no data given. (Polyenes versus placebo).</td>
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<tr>
<td>Nicholl</td>
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<td>No suitable outcomes for review. (Amphotericin B - two doses).</td>
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<td>Niibe</td>
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<td>No clear mucositis index presented. (Amifostine versus placebo).</td>
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Characteristics of excluded studies (Continued)

Okuno 1997  Major change to protocol half way through study. (Antibiotic lozenge versus placebo).
Okuno 1998  Abstract, insufficient information. (Glutamine versus placebo).
Pfeiffer 1989 Abstract, insufficient information. (Sucralfate versus placebo).
Prada 1985  Data not in suitable form. Mean (SD) mucositis scores presented (unsure if RCT). (Benzydamine versus placebo mouthwash).
Raether 1989 Data not in suitable form. Mean (SD) of ulceration over 7 sites per patient presented. (Chlorhexidine versus placebo).

Rocke 1993  Patients returning for a second course of chemo were crossed over to alternate group. This only happened if they experienced no worse than mild mucositis from first course of chemo. Therefore both parallel group and cross-over trial, also biased as only selected patients crossed over. (Ice chips (30 mins) versus Ice chips (60 mins)).
Rutkauskas 1993 Data not in suitable form. Mucositis mean (not SD) presented. (Chlorhexidine versus placebo).
Samaranayake 1988 Data not in suitable form. Mean (not SD) presented. (Benzydamine versus chlorhexidine).
Sato 1997   Unsure if RCT and author has not responded to letter requesting further information.
Suc 1999    Abstract, insufficient information. (Chewing gum versus no treatment).
Vacha 1999  Mucositis scores presented, data not in suitable form for the review. (Amifostine versus no treatment).
Verdi 1995  Data not in suitable form. Oral assessment scores (0-24 scale) presented for each patient. (Pentoxifylline versus placebo).
Weisdorf 1989 Data not in suitable form. Mean (SD) maximal area of ulceration presented. (Chlorhexidine versus placebo).
Wymenga 1999 Abstract, insufficient information. (TGF-B3 mouthrinse versus no treatment).

ADDITIONAL TABLES

Table 01. Quality assessment of trials

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<th>outcome blinded</th>
<th>explanation drop out</th>
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<td>outcome blinded</td>
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</tr>
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### Table 01. Quality assessment of trials (Continued)

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<td>Shenep 1988</td>
<td>A</td>
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<tr>
<td>Spijkervet 1989</td>
<td>B</td>
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<td>Symonds 1996</td>
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<td>Van der Lelie 2001</td>
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<td>Wåhlin 1989</td>
<td>A (B)</td>
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<td>Yuen 2001</td>
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### Table 02. Data from parallel group studies for comparisons involving cross-over studies

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<tr>
<th>Comparison</th>
<th>Treatment n</th>
<th>Treatment N</th>
<th>Control n</th>
<th>Control N</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Glutamine 0 vs 1+</td>
<td>8</td>
<td>8</td>
<td>9</td>
<td>9</td>
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</tr>
<tr>
<td>Okuno 1999</td>
<td>46</td>
<td>66</td>
<td>44</td>
<td>68</td>
<td>1.25 (0.61, 2.59)</td>
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<tr>
<td>Glutamine 0-1 vs 2+</td>
<td>19</td>
<td>29</td>
<td>18</td>
<td>29</td>
<td>1.16 (0.40, 3.39)</td>
</tr>
<tr>
<td>Dickson 2000</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>9</td>
<td>0.88 (0.05, 16.75)</td>
</tr>
<tr>
<td>Okuno 1999</td>
<td>19</td>
<td>66</td>
<td>20</td>
<td>68</td>
<td>0.97 (0.46, 2.05)</td>
</tr>
<tr>
<td>Glutamine 0-2 vs 3+</td>
<td>0</td>
<td>8</td>
<td>4</td>
<td>9</td>
<td>0.07 (0.00, 1.62)</td>
</tr>
<tr>
<td>Okuno 1999</td>
<td>4</td>
<td>66</td>
<td>5</td>
<td>68</td>
<td>0.81 (0.21, 3.17)</td>
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<tr>
<td>Ice chips 0 vs 1+</td>
<td>14</td>
<td>44</td>
<td>20</td>
<td>40</td>
<td>0.47 (0.19, 1.13)</td>
</tr>
<tr>
<td>Cascinu 1994</td>
<td>8</td>
<td>44</td>
<td>14</td>
<td>40</td>
<td>0.41 (0.15, 1.13)</td>
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<tr>
<td>Ice chips 0-2 vs 3+</td>
<td>4</td>
<td>44</td>
<td>10</td>
<td>40</td>
<td>0.30 (0.09, 1.05)</td>
</tr>
<tr>
<td>Cengiz 1999</td>
<td>18</td>
<td>18</td>
<td>10</td>
<td>10</td>
<td>Not estimable</td>
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<tr>
<td>Ice chips 0-1 vs 2+</td>
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<tr>
<td>Sucralfate 0 vs 1+</td>
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<tr>
<td>Cengiz 1999</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>18</td>
<td>0.11 (0.01, 1.07)</td>
</tr>
</tbody>
</table>

*Interventions for preventing oral mucositis for patients with cancer receiving treatment (Review)*

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Table 03. Data from cross-over studies

<table>
<thead>
<tr>
<th>Comparison</th>
<th>test-/control-</th>
<th>test-/control+</th>
<th>test+/control-</th>
<th>test+/control+</th>
<th>OR (95% CI)</th>
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<td>allupurinol mouthrinse 0 vs 1+</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>4</td>
<td>0.00 (0.00, 0.45)</td>
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<tr>
<td>Dozono 1989 (low)</td>
<td>0</td>
<td>11</td>
<td>1</td>
<td>3</td>
<td>0.09 (0.002, 0.63)</td>
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<tr>
<td>Loprinzi 1990</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>9</td>
<td>0.50 (0.05, 3.49)</td>
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<tr>
<td>allupurinol mouthrinse 0-1 vs 2+</td>
<td>4</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0.00 (0.00, 0.40)</td>
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<tr>
<td>Dozono 1989</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>1.25 (0.27, 6.30)</td>
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<td>8</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0.00 (0.00, 0.69)</td>
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<tr>
<td>Loprinzi 1990</td>
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<td>3</td>
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<td>0.00 (0.00, 2.42)</td>
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<tr>
<td>glutamine 0 vs 1+</td>
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<td>5</td>
<td>0</td>
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<td>0.00 (0.00, 1.09)</td>
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<td>2</td>
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<td>9</td>
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<td>3</td>
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<td>0.00 (0.00, 2.42)</td>
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Table 03. Data from cross-over studies (Continued)

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<tr>
<th>Comparison</th>
<th>test-/control-</th>
<th>test-/control+</th>
<th>test+/control-</th>
<th>test+/control+</th>
<th>OR (95% CI)</th>
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</tr>
<tr>
<td>Mahood 1991</td>
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<td>1</td>
<td>0.00 (0.00, 0.69)</td>
</tr>
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<td>sucralfate 0-2 vs 3+</td>
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<tr>
<td>Pfeiffer 1990 (low)</td>
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Table 04. Results from parallel group and cross-over studies

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<td>Dozono 1989 (low)</td>
<td>0.00 (0.00, 0.45)</td>
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<tr>
<td>Dozono 1989 (high)</td>
<td>0.09 (0.002, 0.63)</td>
<td>Q=6.68, 1df, p=0.01</td>
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<tr>
<td>Loprinzi 1990</td>
<td>0.50 (0.05, 3.49)</td>
<td>Q=0.88, 1df, p=0.34</td>
</tr>
<tr>
<td>Pooled results (Dozono low)</td>
<td>0.03 (0.00, 12.7) p=0.26</td>
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<tr>
<td>(Dozono high)</td>
<td>0.271 (0.05, 1.51) p=0.14</td>
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<td>allopurinol mouthrinse 0-1 vs 2+</td>
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<td>Dozono 1989</td>
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<tr>
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<td>Loprinzi 1990</td>
<td>0.00 (0.00, 2.42)</td>
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<td>Pooled results</td>
<td>0.00 (0.03) p&lt;0.001</td>
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<td>Jebb 1994 (high)</td>
<td>0.75 (0.21, 2.47)</td>
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<td>Okuno 1999</td>
<td>1.25 (0.61, 2.59)</td>
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<td>Pooled results (Jebb low)</td>
<td>0.01 (0.00, 4.24) p=0.14</td>
<td>Q=31.24, 2df, p&lt;0.001</td>
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<td>0.43 (0.07, 2.72) p=0.37</td>
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<td>glutamine 0-1 vs 2+</td>
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<td>Dickson 2000</td>
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<td>Huang 2000</td>
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<td>Jebb 1994 (low)</td>
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<td>Study Year</td>
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<td>Glutamine 0-2 vs 3+</td>
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<td>0.98 (0.48, 2.00)</td>
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<td>Mahood 1991</td>
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ANALYSES

Comparison 01. Active treatment versus placebo/no treatment

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<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
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<td>01 mucositis (absent versus present)</td>
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Comparison 02. Side effects

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<td>01 amifostine</td>
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INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Administration, Topical; Antifungal Agents [*therapeutic use]; Antineoplastic Agents [*adverse effects]; Candidiasis, Oral [*chemically induced; etiology; *prevention & control]; Cryotherapy; Ice; Mouth Mucosa; Neoplasms [drug therapy; radiotherapy]; Randomized Controlled Trials; Stomatitis [*chemically induced; etiology; *prevention & control]

MeSH check words

Humans

COVER SHEET

Title
Interventions for preventing oral mucositis for patients with cancer receiving treatment

Authors
Clarkson JE, Worthington HV, Eden OB

Contribution of author(s)
Jan Clarkson (JC) and Helen Worthington (HW) wrote the protocol and review. HW coordinated the review and wrote the letters to authors. JC and HW independently and in duplicate assessed the eligibility of trials, extracted data and assessed the quality of the trials. Tim Eden (OE) provided advice on cancer, its treatment and the interventions included in the review and checked the data. HW conducted the statistical analysis.

Issue protocol first published
1998/1

Review first published
2000/1

Date of most recent amendment
21 May 2004

Date of most recent SUBSTANTIVE amendment
23 May 2003

What's New
This is an update of the Cochrane Review 'Prevention of oral mucositis or oral candidiasis for patients with cancer receiving chemotherapy'. This update concentrates on oral mucositis and the breadth of the review has been extended to include all types of cancer and its treatment, and any interventions and comparisons between them.

Date new studies sought but none found
Information not supplied by author
Analysis 01.01. Comparison 01 Active treatment versus placebo/no treatment, Outcome 01 mucositis (absent versus present)

Review: Interventions for preventing oral mucositis for patients with cancer receiving treatment
Comparison: 01 Active treatment versus placebo/no treatment
Outcome: 01 mucositis (absent versus present)

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<th>Weight (%)</th>
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### Analysis 01.02. Comparison 01 Active treatment versus placebo/no treatment, Outcome 02 mucositis (0-1 versus 2+)

**Review:** Interventions for preventing oral mucositis for patients with cancer receiving treatment

**Comparison:** 01 Active treatment versus placebo/no treatment

**Outcome:** 02 mucositis (0-1 versus 2+)

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*Interventions for preventing oral mucositis for patients with cancer receiving treatment (Review)*

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### Analysis 01.03. Comparison 01 Active treatment versus placebo/no treatment, Outcome 03 mucositis (0-2 versus 3+)

**Review:** Interventions for preventing oral mucositis for patients with cancer receiving treatment

**Comparison:** 01 Active treatment versus placebo/no treatment

**Outcome:** 03 mucositis (0-2 versus 3+)

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Test for heterogeneity chi-square=26.01 df=4 p=<0.0001 I² =84.6%

Test for overall effect z=1.79  p=0.07

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Relative Risk (Random)</th>
<th>Weight (%)</th>
<th>Relative Risk (Random)</th>
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<tr>
<td>Wijers 2001</td>
<td>15/39</td>
<td>18/38</td>
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<td>100.0</td>
<td>0.81 [0.48, 1.37]</td>
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<td>38</td>
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Test for heterogeneity: not applicable

Test for overall effect z=0.79  p=0.4

### (Continued...)

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*Interventions for preventing oral mucositis for patients with cancer receiving treatment (Review)*

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<table>
<thead>
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<th>Interventions</th>
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<th>n/N</th>
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<th>Weight (%)</th>
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<tr>
<td>03 camomile versus placebo</td>
<td>Fidler 1996</td>
<td>8/82</td>
<td>7/82</td>
<td>1.14 [0.43, 3.01]</td>
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<td>1.14 [0.43, 3.01]</td>
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<tr>
<td>Test for overall effect z=0.27</td>
<td>p=0.8</td>
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<tr>
<td>04 chlorhexidine versus placebo or no treatment</td>
<td>Foote 1994</td>
<td>14/25</td>
<td>15/27</td>
<td>1.01 [0.62, 1.64]</td>
<td>28.7</td>
<td>1.00 [0.70, 1.43]</td>
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<td>Spijkeret 1989</td>
<td>12/15</td>
<td>12/15</td>
<td>52.5</td>
<td>1.00 [0.70, 1.43]</td>
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<td>Wahlin 1989</td>
<td>8/14</td>
<td>9/14</td>
<td>18.8</td>
<td>0.89 [0.49, 1.62]</td>
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<td>p=0.9</td>
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<td>05 folinic acid versus no treatment</td>
<td>Erlichman 1988</td>
<td>4/64</td>
<td>0/61</td>
<td>8.58 [0.47, 156.17]</td>
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<td>06 GM-CSF versus placebo</td>
<td>Cartee 1995</td>
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<td>2/9</td>
<td>1.88 [0.52, 6.76]</td>
<td>24.0</td>
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<td>Nemunaitis 1995</td>
<td>4/53</td>
<td>16/56</td>
<td>27.4</td>
<td>0.26 [0.09, 0.74]</td>
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<tr>
<td>Schneider 1999</td>
<td>1/8</td>
<td>3/6</td>
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<td>0.25 [0.03, 1.85]</td>
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<td>Van der Leslie 2001</td>
<td>11/18</td>
<td>8/18</td>
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<td>df=3</td>
<td>p=0.01</td>
<td>I² =72.2%</td>
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<td>p=0.5</td>
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<tr>
<td>07 hydrolytic enzymes versus no treatment</td>
<td>Gujral 2001</td>
<td>3/53</td>
<td>15/46</td>
<td>0.17 [0.05, 0.56]</td>
<td>86.6</td>
<td>0.17 [0.05, 0.56]</td>
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<tr>
<td>Kaul 1999</td>
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<td>2/25</td>
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<td>0.20 [0.01, 3.97]</td>
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<td>Subtotal (95% CI)</td>
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<td>71</td>
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<td>I² =0.0%</td>
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<td>Test for overall effect z=3.10</td>
<td>p=0.002</td>
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<tr>
<td>08 oral care (intensive oral hygiene versus limited oral hygiene)</td>
<td>Borowski 1994</td>
<td>49/75</td>
<td>58/75</td>
<td>0.84 [0.69, 1.04]</td>
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<td>0.84 [0.69, 1.04]</td>
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</table>

Favours treatment Favours control (Continued . . . )

Interventions for preventing oral mucositis for patients with cancer receiving treatment (Review)
Copyright © 2006 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Random)</th>
<th>Weight (%)</th>
<th>Relative Risk (Random)</th>
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<tbody>
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<td>0.9 povidone versus water</td>
<td>4/20</td>
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<td>0.31 [0.12, 0.78]</td>
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<td>10 prednisone versus placebo</td>
<td>3/32</td>
<td>5/34</td>
<td>0.64 [0.17, 2.45]</td>
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<tr>
<td>11 prostaglandin versus placebo</td>
<td>17/31</td>
<td>15/29</td>
<td>1.06 [0.66, 1.70]</td>
<td>100.0</td>
<td>1.06 [0.66, 1.70]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>31</td>
<td>29</td>
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Test for heterogeneity: not applicable
Test for overall effect z=0.24 p=0.8

Subtotal (95% CI) 75 75
Total events: 49 (Treatment), 58 (Control)
Test for overall effect z=1.61 p=0.1

Test for overall effect z=2.47 p=0.01
### Analysis 02.01. Comparison 02 Side effects, Outcome 01 amifostine

**Review:** Interventions for preventing oral mucositis for patients with cancer receiving treatment

**Comparison:** 02 Side effects

**Outcome:** 01 amifostine

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Relative Risk (Random) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Random) 95% CI</th>
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</thead>
<tbody>
<tr>
<td><strong>01 survival at 24 months</strong></td>
<td></td>
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</tr>
<tr>
<td>Brizel 2000</td>
<td>30/36</td>
<td>22/30</td>
<td>95% CI</td>
<td>29.1</td>
<td>1.14 [ 0.88, 1.47 ]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>30</td>
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<td>29.1</td>
<td>1.14 [ 0.88, 1.47 ]</td>
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<td><strong>02 recurrence at 18 months after cancer treatment</strong></td>
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</tr>
<tr>
<td>Antonadou 2002</td>
<td>4/22</td>
<td>6/23</td>
<td>Relative Risk (Random) 95% CI</td>
<td>7.9</td>
<td>0.70 [ 0.23, 2.14 ]</td>
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<td>Brizel 2000</td>
<td>28/80</td>
<td>28/88</td>
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<td><strong>03 incomplete response to radiotherapy</strong></td>
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<td>5/23</td>
<td>Relative Risk (Random) 95% CI</td>
<td>4.7</td>
<td>0.42 [ 0.09, 1.94 ]</td>
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<td>Koukourakis 2000</td>
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<td>6/12</td>
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<td><strong>04 delay to radiotherapy</strong></td>
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<td>Antonadou 2002</td>
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<td>0/23</td>
<td>Relative Risk (Random) 95% CI</td>
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<td>7.30 [ 0.40, 133.75 ]</td>
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<tr>
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<td>4/148</td>
<td>0/153</td>
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<td>9.30 [ 0.51, 171.28 ]</td>
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<tr>
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<td>176</td>
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<td>2.9</td>
<td>8.24 [ 1.05, 64.52 ]</td>
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| Test for heterogeneity: not applicable |
| Test for overall effect z=0.06 p=0.3 |

| Test for heterogeneity: chi-square=0.56 df=1 p=0.46 I²=0% |
| Test for overall effect z=0.18 p=0.9 |

| Test for heterogeneity: chi-square=0.63 df=1 p=0.43 I²=0% |
| Test for overall effect z=0.91 p=0.4 |

| Test for heterogeneity: not applicable |
| Test for overall effect z=1.94 p=0.05 |

| Test for heterogeneity: chi-square=0.01 df=1 p=0.91 I²=0% |
| Test for overall effect z=2.01 p=0.04 |

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

(Continued...)
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<td>n/N</td>
<td>95% CI (%)</td>
<td>(%)</td>
<td>95% CI (%)</td>
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<tr>
<td>06 nausea</td>
<td></td>
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<tr>
<td>Antonadou 2002</td>
<td>1/22</td>
<td>0/23</td>
<td></td>
<td>1.2</td>
<td>3.13 [ 0.13, 72.99 ]</td>
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<td>1.3</td>
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<td>1/153</td>
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<td>188</td>
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<td>0/23</td>
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<td>0/153</td>
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Interventions for preventing oral mucositis for patients with cancer receiving treatment (Review)

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<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
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<th>Relative Risk (Random)</th>
<th>95% CI</th>
<th>Test for heterogeneity</th>
<th>Test for overall effect</th>
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<td>95% CI</td>
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<td>Makkonen 2000</td>
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<td>31.4</td>
<td>0.73</td>
<td>0.46, 1.17</td>
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Test for overall effect: z=0.65 p=0.5

Favours treatment Favours control

Interventions for preventing oral mucositis for patients with cancer receiving treatment (Review)

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