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

Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, McCabe MG, Meyer S, Khalid T

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[Intervention Review]

Interventions for preventing oral mucositis for patients with cancer receiving treatment

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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 methods

Electronic searches of Cochrane Oral Health Group and PaPaS Trials Registers (to 16 February 2011), CENTRAL (*The Cochrane Library* 2011, Issue 1), MEDLINE via OVID (1950 to 16 February 2011), EMBASE via OVID (1980 to 16 February 2011), CINAHL via EBSCO (1980 to 16 February 2011), CANCERLIT via PubMed (1950 to 16 February 2011), OpenSIGLE (1980 to 2005) and LILACS via the Virtual Health Library (1980 to 16 February 2011) were undertaken. Reference lists from relevant articles were searched and the authors of eligible trials were contacted to identify trials and obtain additional information.

Selection criteria

Randomised controlled trials of interventions to prevent oral mucositis in patients receiving treatment for cancer.

Data collection and analysis

Information regarding methods, participants, interventions, outcome measures, results and risk of bias were independently extracted, in duplicate, by two review authors. Authors were contacted for further details where these were unclear. The Cochrane Collaboration statistical guidelines were followed and risk ratios calculated using random-effects models.

Main results

A total of 131 studies with 10,514 randomised participants are now included. Overall only 8% of these studies were assessed as being at low risk of bias. Ten interventions, where there was more than one trial in the meta-analysis, showed some statistically significant evidence of a benefit (albeit sometimes weak) for either preventing or reducing the severity of mucositis, compared to either a placebo or no treatment. These ten interventions were: aloe vera, amifostine, cryotherapy, granulocyte-colony stimulating factor (G-CSF), intravenous glutamine, honey, keratinocyte growth factor, laser, polymixin/tobramycin/amphotericin (PTA) antibiotic pastille/paste and sucralfate.

Authors' conclusions

Ten interventions were found to have some benefit with regard to 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 further well designed, and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent.

PLAIN LANGUAGE SUMMARY

Interventions for preventing oral mucositis for patients with cancer receiving treatment

Treatment for cancer (including bone marrow transplant) can cause oral mucositis (severe ulcers in the mouth). This painful condition can cause difficulties in eating, drinking and swallowing, and may also be associated with infections which may require the patient to stay longer in hospital. Different strategies are used to try and prevent this condition, and the review of trials found that some of these are effective. Two interventions, cryotherapy (ice chips) and keratinocyte growth factor (palifermin®) showed some benefit in preventing mucositis. Sucralfate is effective in reducing the severity of mucositis, and a further seven interventions, aloe vera, amifostine, intravenous glutamine, granulocyte-colony stimulating factor (G-CSF), honey, laser and antibiotic lozenges containing polymixin/tobramycin/amphotericin (PTA) showed weaker evidence of benefit. These were evaluated in patients with different types of cancer, undergoing different types of cancer treatment. Benefits may be restricted to the disease and treatment combinations evaluated.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Cryotherapy versus no treatment for preventing oral mucositis for patients with cancer receiving treatment

Patient or population: preventing oral mucositis for patients with cancer receiving treatment
Settings:
Intervention: Cryotherapy versus no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Cryotherapy versus no treatment				
Mucositis (any) 0-4 scale Follow-up: median 28 days	**Low risk population**[1]		**RR 0.74** (0.57 to 0.95)	472 (5 studies)	⊕⊕◯◯ **low**[2,3]	
	600 per 1000	**444 per 1000** (342 to 570)				
	High risk population[1]					
	950 per 1000	**703 per 1000** (541 to 902)				
Mucositis (severe) 0-4 scale Follow-up: median 28 days	**Low risk population**[4]		**RR 0.36** (0.17 to 0.77)	472 (5 studies)	⊕⊕◯◯ **low**[2,5]	
	300 per 1000	**108 per 1000** (51 to 231)				
	High risk population[4]					
	650 per 1000	**234 per 1000** (111 to 501)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Based on the range of absolute risk of developing any mucositis of patients (with different cancer types and treatments) in the control groups of the included studies.
[2] 3 studies at high risk of bias and 2 unclear
[3] Substantial heterogeneity Chi squared = 14.77, df=4, P=0.005, I squared =73%,
[4] Based on the range of absolute risk of developing severe mucositis of patients (with different cancer types and treatments) in the control groups of the included studies.
[5] Substantial heterogeneity Chi squared=14.31, df=4, P=0.006, I squared =72%.

BACKGROUND

Treatment for malignancies with cytotoxic chemotherapy or radiotherapy or both are becoming increasingly effective but are 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 or pain, poor nutrition, delays in cancer treatment, 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 plethora of prophylactic agents, many of which are not evidence based. Individual cancer centres use different mouth care regimens to prevent mucositis (Glenny 2004), frequently with scant evidence of efficacy. Mucositis presents a particular challenge due to its complex biological nature and the range of interventions tested have included mucosal surface protectants, anti-inflammatory formulations, antimicrobials, growth factors and a plethora of other miscellaneous agents. Given the costs to patients and their clinicians of mucositis-related morbidity it is surprising that a uniform approach to mucositis prevention, backed by a strong evidence base, is lacking. There are variations in usage between cancer centres in terms of the mouth care 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 (Andreassen 2003; Chang 2003; De Pauw 1997; Denning 1992; Duncan 2003; Lortholary 1997; Savarese 2003; 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. Three systematic reviews have focused on the prevention of oral mucositis in patients with cancer (Kowanko 1998; Stokman 2006; Sunderland 2001). Kowanko and colleagues concluded that for most strategies reviewed there was insufficient evidence to draw any conclusions regarding their effectiveness (Kowanko 1998). Sunderland and colleagues focused exclusively on patients with head and neck cancer. Their main analysis combined all the interventions in one meta-analysis and found a beneficial effect of prophylactic interventions (Sunderland 2001). The most recent published review (Stokman 2006) considered eight different interventions and found four which showed a statistically significant effect in preventing the development or severity of mucositis. Since the previous update of this review the most significant development in this field have been the publication of a review of evidence and the development of clinical practice guidelines by the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (Keefe 2007; Rubenstein 2004; Sonis 2004). The development of clinical practice guidelines highlights the fact that preventing and managing mucositis in cancer patients worldwide is imperative. However, given the large number of clinical trials identified in this systematic review, it is important that researchers work co-operatively to maintain up to date systematic reviews, which can then be used to provide the evidence base for clinical guidelines, which can be adapted at the local level to take account of policy and resources.

A previous version of this Cochrane review looked at the use of prophylactic agents for the prevention of oral mucositis and oral candidiasis in patients with cancer treated by chemotherapy (Clarkson 2000). The review concluded that there was some evidence that using ice chips during the chemotherapy treatment was effective in preventing mucositis. The review was updated in 2003 (Clarkson 2003a) and this update broadened the oral mucositis part of the initial review and looked at the prevention of oral mucositis in patients receiving any treatment for cancer, including patients with all types of cancer, as well as head and neck cancer, and including comparisons between any interventions for prevention. A second review update was carried out in 2006 (Worthington 2006) and reviews on the prevention of oral candidiasis have also been published in *The Cochrane Library* (Clarkson 2007a; Worthington 2004a). The third prevention review update was carried out in 2007 (Worthington 2007).These reviews form part of a series of Cochrane reviews on the prevention and treatment of oral mucositis, oral candidiasis (Clarkson 2007b; Worthington 2007a); xerostomia (Tavender 2004) and herpes simplex in patients receiving cancer therapy (Glenny 2009).

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 radiotherapy, chemotherapy or targeted therapies.

We also investigated the following secondary outcomes for benefits or harms provided there were three or more trials or one trial with more than 100 participants, otherwise we recorded outcomes reported:

- Oral hygiene measures
- Relief of pain/use of analgesia
- Duration or severity of dysphagia
- Use of parenteral nutrition or feeding tube
- Incidence of systemic infection or use of antibiotics

- Febrile episodes
- Blood changes
- Treatment interruption
- Days of stay in hospital
- Toxicity (nausea/vomiting/constipation/diarrhoea)
- Toxicity - skin changes
- Toxicity - unspecific
- Xerostomia
- Cost of care
- Patient quality of life
- Death
- Weight loss/gain
- Caloric intake by oral nutrition
- Eating/drinking difficulty
- Overall health
- Recurrence of cancer.

The following subgroup analyses were proposed:

- Cancer type (leukaemia, head and neck, other solid tumours and mixed)
- Cancer treatment (specific, for example 5-fluorouracil (5-FU))
- Age group (adults, children or both).

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were eligible for inclusion in this review, including both cross-over and parallel group studies.

Types of participants

Anyone with cancer who received radiotherapy, chemotherapy or targeted therapies.

Types of interventions

(This review did not include studies of different cancer treatments when the primary outcome was survival or cure with mucositis as a toxicity.)
Active agents: any agent prescribed as prophylaxis for oral mucositis.
Control: may be placebo or no treatment, or another active intervention.

Types of outcome measures

Primary outcome

- Mucositis (at all levels of severity) (ulcers). Mucositis measured on a 0 to 4 point scale (none to severe) was used and this was dichotomised as any mucositis (0 versus 1+), moderate plus severe mucositis (0 to 1 versus 2+), severe mucositis (0 to 2 versus 3+).

- Trials where mucositis is measured using a scale which individually grades multiple components of oral health such as teeth or plaque (Eilers 1988), are excluded. It is acknowledged that these oral effects are important, but it is not possible to separate the 'mucositis only' score, from the total score, so this review will not include studies which evaluate mucositis using such component scores.

Secondary outcomes

- Oral hygiene measures
- Relief of pain/use of analgesia
- Duration or severity of dysphagia
- Use of parenteral nutrition or feeding tube
- Incidence of systemic infection or use of antibiotics
- Febrile episodes
- Blood changes
- Treatment interruption
- Days of stay in hospital
- Toxicity (nausea/vomiting/constipation/diarrhoea)
- Toxicity - skin changes
- Toxicity - unspecific
- Xerostomia
- Cost of care
- Patient quality of life
- Death
- Weight loss/gain
- Caloric intake by oral nutrition
- Eating/drinking difficulty
- Overall health
- Recurrence of cancer.

Search methods for identification of studies

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 strategies were used for all four reviews.

The searches attempted to identify all relevant trials irrespective of language. Papers not in English were translated by members of The Cochrane Collaboration. Sensitive search strategies were developed for each database using a combination of free text and MeSH terms. The MEDLINE and CANCERLIT searches combined the subject search with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2009 revision) as referenced in Chapter 6.4.11.1 and detailed in boxes 6.4.a and 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.0.2 (updated September 2009) (Higgins 2009). The EMBASE and CINAHL searches were combined with sensitive search strategies developed by the Cochrane Oral Health Group for identifying randomised controlled trials (RCTs). The LILACs subject search was combined with the Brazilian Cochrane Centre search strategy for identifying RCTs in LILACS.

Electronic searching - the databases searched were:

- Cochrane Oral Health Group Trials Register (to 16 February 2011) (Appendix 1)
- Cochrane Pain, Palliative and Supportive Care (PaPaS) Group Trials Register (to 16 February 2011) (Appendix 1)
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1) (Appendix 2)
- MEDLINE via OVID (1950 to 16 February 2011) (Appendix 3)
- EMBASE via OVID (1980 to 16 February 2011) (Appendix 4)
- CANCERLIT via PubMed (1950 to 16 February 2011) (Appendix 5)
- OpenSIGLE (1980 to 2005) (Appendix 6)
- LILACS via The Virtual Health Library (to 16 February 2011) (Appendix 7)
- CINAHL via EBSCO (1980 to 16 February 2011) (Appendix 8).

Only handsearching carried out by The Cochrane Collaboration was included in the search (*see* master list www.cochrane.org).

The controlled trials database (www.controlled-trials.com) was also searched to identify ongoing and completed trials and to contact trialists for further information about these trials.

The reference list of related review articles and all articles obtained were checked for further trials. Authors of trial reports and specialists in the field known to the review authors were written to concerning further published and unpublished trials.

The review will be updated every 2 years using the Cochrane Oral Health Group Trials Register, CENTRAL, MEDLINE, EMBASE, CINAHL, CANCERLIT and LILACS. The search of OpenSIGLE was discontinued as this database ceased being updated in 2005.

Data collection and analysis

Selection of studies

The titles and abstracts (when available) of all reports identified through the electronic searches were scanned independently by two review authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. The full reports, containing names of the authors, institutions, journal of publication and results, obtained from all the electronic and other methods of searching were assessed independently by two authors with expertise in this content area, to establish whether the studies met the inclusion criteria or not. Disagreements were resolved by discussion. Where resolution was not possible, a third review author was consulted. All studies meeting the inclusion criteria then underwent validity assessment and data extraction. Studies rejected at this or subsequent stages were recorded in the 'Characteristics of excluded studies' table, and reasons for exclusion recorded.

Data extraction and management

Data were extracted by two review authors 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. We planned to form three dichotomies of mucositis: absent versus present (0 versus 1+), mild versus moderate/severe (0 to 1 versus 2+) and moderate versus severe (0 to 2 versus 3+). 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.

Assessment of risk of bias in included studies

For any relevant studies identified, two review authors independently graded the relevant trials following the domain-based evaluation described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.2 (updated September 2009) (Higgins 2009). The review authors then compared evaluations, discussed and resolved any disagreements and reported their assessments in a risk

of bias in included studies table in Review Manager (RevMan) software.

An assessment of the overall risk of bias involved the consideration of the relative importance of different domains and studies were to be categorised as low, high or unclear risk of bias.

The review authors were to assess the following domains as 'Yes' (i.e. low risk of bias), 'Unclear' (i.e. uncertain risk of bias) or 'No' (i.e. high risk of bias):

1. adequate sequence generation;
2. allocation concealment;
3. blinding (of participants, carers and outcome assessors);
4. incomplete outcome data addressed;
5. free of selective outcome reporting;
6. free of other bias.

These risk of bias assessments were then for each study across all domains. Adequate allocation concealment and blinding of outcome assessors were designated as key domains for this assessment. Overall risk of bias was categorised according to the following:

- Low risk of bias (plausible bias unlikely to seriously alter the results) for all key domains;
- Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more key domains were assessed as unclear; or
- High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more key domains were assessed to be at high risk of bias.

Measures of treatment effect

For dichotomous outcomes, the estimate of effect of an intervention was expressed as risk ratios (RR) together with 95% confidence intervals (CIs). For continuous outcomes, mean differences and standard deviations were used to summarise the data for each group using mean differences and 95% CIs. Appropriate data were extracted from the cross-over studies and the generic inverse variance method was used to enter this into RevMan.

Unit of analysis issues

The patient was the unit of analysis in all trials.

Dealing with missing data

All authors were contacted to retrieve missing data from authors of trials.

The analysis will generally include only the available data (ignoring missing data) however methods for estimating missing standard deviations in Section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.2 (Higgins 2009) were to be used. Otherwise we do not intend to undertake any imputations nor to use statistical methods to allow for missing data.

Assessment of heterogeneity

The significance of any discrepancies in the estimates of the treatment effects from the different trials was to be assessed by means of Cochran's test for heterogeneity and heterogeneity would have been considered significant if $P < 0.1$ (Higgins 2009).

The I^2 statistic, which describes the percentage total variation across studies that is due to heterogeneity rather than chance, was used to quantify heterogeneity with I^2 over 50% being considered substantial heterogeneity (Higgins 2009; Section 9.5.2). In order to assist in the readers in the interpretation of heterogeneity we would still have included the pooled meta-analysis in the forest plot because the I^2 and Chi^2 statistics are helpful. With substantial heterogeneity pooling the data may not be appropriate and this will be considered in the results for each intervention.

Assessment of reporting biases

If there had been sufficient numbers of trials (more than 10) in any meta-analysis, publication bias would have been assessed according to the recommendations on testing for funnel plot asymmetry (Egger 1997) as described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.2 (Higgins 2009). If asymmetry were identified we would have examined possible causes.

Data synthesis

A meta-analysis would have only be conducted if there were studies of similar comparisons reporting the same mucositis outcome measures. Single studies would not be entered into forest plots. Risk ratios were to be combined for dichotomous data, and mean differences for continuous data, using random-effect models provided there were more than three studies in the meta-analysis.

It is possible to conduct cross-over trials in this area as patients may be receiving several chemotherapy sessions, any mucositis completely healing in the periods between the sessions. 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 (Elbourne 2002). The generic inverse variance method incorporated in RevMan was used for all analyses. Where data for the cross-tabulation of pairs were not available, all possible paired comparisons for each study were calculated, giving rise to the same risk ratios values with different confidence intervals. The widest confidence interval was used in the analysis.

Subgroup analysis and investigation of heterogeneity

Clinical heterogeneity was to be assessed by examining the types of participants and interventions for all outcomes in each study. We proposed a priori to conduct subgroup analyses for different cancer types (leukaemia, head and neck, other solid tumours and mixed), cancer treatment (for example 5-fluorouracil (5-FU)) and age groups (children, adults and both). However, there were insufficient trials by intervention type to do this.

Sensitivity analysis

It was planned to undertake sensitivity analyses to examine the effect of the study quality assessment on the overall estimates of effect. In addition, the effect of including unpublished literature on the review's findings was also to be examined. There were too few trials to undertake these analyses.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Characteristics of the trial settings and investigators

Three hundred and eighty-three reports of trials were initially identified as eligible according to the defined inclusion criteria for this review with regard to study design, participants, interventions and outcomes. From this list, the total number of included trials was 131, there were 10 duplicate reports and 176 studies were excluded.

See Characteristics of excluded studies table for further information on each excluded study. In summary, studies were excluded for the following reasons.

- Abstracts only available, insufficient information to include study in the review (36 studies: Antonadou 1998; Buentzel 1999; Castro 2009; Clarke 2001; Collova 2004; Colombat 1995; Costa 1999; Gabison 1995; Goldberg 2003; Gordon 1993; Harris 1995; He 2004; Kante 1995; Klocke 2006; Lavendag 1998; Le 2008; Leong 1995; Lozada 1998; Marcial 1994; Merte 1999; Papas 1984; Pouli 1999; Radmard 2002; Robustelli 1999; Schwerkoske 1999; Sharma 2009; Shea 2007; Shidfar 2008; Spadaro 1991; Spielberger 2001; Throuvalas 1995; Valcárcel 1997; Vesole 1999; Villar 2009; Vitello 2000; Wagner 2002).
- Comparing different cancer treatments including radiotherapy regimens (29 trial reports: Andersen 1987; Ardizzoni 2002; Awada 2002; Awwad 2002; Bensadoun 2006; Bentzen 2001; Bleehen 1996; Bourhis 2006; Calais 2000; Cassidy 2002; Cunningham 1995; Damon 2004; De Boer 2002; Denham 1999; Dobrowsky 1998; Doroshow 1987; Erkisi 1996; Erlichman 1988; Ezzat 2005; Falcone 2001; Giles 2003a; Giles 2003b; Gladkov 2007; Lee 1989; Levi 1997; Mahmoud 1996; Pyrhonen 1995; Rabinovitch 2006; Rocci 2005).
- Not a randomised controlled trial (64 study reports: Aisa 2005; Altmann 1999; Arora 2008; Awada 2004; Baydar 2005; Calais 2004; Cheng 2001; Cheng 2002; Colella 2010; Costa 2003; Dreicer 1997; Edelman 1998; Eisen 2003; El-Sayed 2002a; Fahlke 1999; Fay 1994; Foncuberta 2001; Gandara 1997; Gutierrez 1996; Horsley 2007; Hu 2003; Hunter 2007; Inagaki 2006; Ito 2002; Johnson 2002; Ju 2009; Karacetin 2004; Khouri 2009; Kuriakose 2002; Labbate 2003; Luglié 2002; Maddocks-Jennings 2009; Madero 1999; Malaker 1991; Mantovani 2003; Martin 2006; Matejka 1990; Mills 1995; Mori 2006; Nicolatou-Galitis 2006; Okutomi 2000; Papadeas 2007; Penpattanagul 2007; Peters 1993; Phillips 2002; Putwatana 2009; Sato 1997; Sato 2006; Schuster 2008; Shabanloei 2009; Simoes 2009; Stokman 2004; Thieblemont 2002; Tiemann 2006; Toubai 2003; Uchiyama 2005; Wang 2002a; Ward 2007; Weiss 1990; Whelan 2002; Whelan 2004; Wollina 2002; Wymenga 1999; Yokomizo 2004).
- Multicomponent oral assessment instruments (which included voice, teeth etc) - specifically excluded in methods section of review (16 trial reports: Aquino 2005; Cowen 1997; Dudjak 1987; Epstein 1992; Etiz 2000; Feber 1995; Feber 1996; Grotz 2001; Jebb 1995; Kenny 1990; McIlroy 1996; Nikoletti 2005; Piccirillo 2003; Pytlik 2002; Rothwell 1990; Verdi 1995).
- Some mucositis present at baseline (12 trial reports: Anderson 1998b; Barasch 1995; Djuric 2006; Ferretti 1990; Genot-Klastersky 2008; Kuhn 2009; Lanzos 2010; Loo 2010; Masucci 2005; Prada 1985; Ryu 2007; Valcarcel 2002).
- Mucositis prevention not purpose of study (one trial report: Jham 2007).
- Data presented as episodes rather than patients, where patients were re-entered into the study, so data not independent (seven trial reports: Abramoff 2008; Awidi 2001; Hickey 1982; Karthaus 1998; Lorusso 2003; Rojas 2001; van Zaanen 1994).
- Major change to protocol half way through study, blinded and unblinded patient data combined (one trial report: Okuno 1997).
- Unclear if mucositis present at baseline (one trial report: Cheng 2006).
- Unclear if randomised (four trial reports: Apaydin 1996; Howell 1983; Teshima 1986; Zanin 2010).
- No mucositis data - study stopped early because preset stooping rule triggered (two trial reports: Antin 2002; Rades 2004).
- No clear mucositis data presented and unable to contact authors (two trial reports: Niibe 1985; Rutkauskas 1993).
- Design flaw - confounded interventions (one trial report: Papas 2003).

Of the 131 included trials 124 were designed as parallel group studies and seven as cross-over studies (Anderson 1998; Chi 1995; Dozono 1989; Jebb 1994; Loprinzi 1990; Mahood 1991; Pfeiffer 1990). None of the published reports of cross-over studies reported the 'paired' data in an appropriate form to be used in a meta-analysis. All the authors were contacted and replies were received supplying data for three studies (Anderson 1998; Loprinzi 1990; Mahood 1991). Data from the other cross-over studies were extracted as outlined in the methods section.

Of the 131 included trials all included data on assessment of mucositis. Ninety-two (70%) of the 131 included trials were con-

ducted at a single site. Thirty-two of these trials were conducted in Europe, 20 in the USA, seven in China, five in India, four in Canada, three in Brazil and Japan, two in Iran, Israel, Thailand, Taiwan and Turkey, and one in each of the following countries: Argentina, Egypt, Hong Kong, Malaysia, Mexico, South Africa, South Korea, and Uruguay. Thirty-six trials were multicentre studies. Ten of these were conducted in the USA (Blazar 2006; Crawford 1999; Dodd 1996; Freytes 2004; Giles 2004; Hanson 1995; Mahood 1991; Meropol 2003; Scarantino 2006; Spielberger 2004), three in the USA and Canada (Epstein 2001; Foote 1994; Nemunaitis 1995), two in the USA and European countries (Brizel 2000; Buentzel 2006), two in European countries alone (Castagna 2001; Vokurka 2005), one in the USA, Canada and Europe (Trotti 2004), one in the USA and Australia (Rosen 2006) and one in the USA, Australia and Canada (Brizel 2008). Two studies were conducted in Australia (Spencer 2005; Veness 2006), Canada (Bjarnason 2009; El Sayed 2002), France (Bensadoun 1999; Gandemer 2007), Iran (Abbasi-Nazari 2007; Motallebnejad 2008) and Taiwan (Chi 1995; Lin 2006), and one in each of the following countries: China (Tu 1998), Germany (Dorr 2007), Italy (Gori 2007), South Korea (Wu 2009), Russia (Peterson 2009) and Thailand (Veerasarn 2006). It was unclear whether the remaining three studies were conducted at a single site or were multisite studies (Bubley 1989; Lievens 1998; Qin 2007). Eighty-one studies (62%) provided funding information. Thirty-seven (28%) trials were funded by the pharmaceutical industry. Twenty-three studies received government funding. Whilst an additional nine trials were funded by a combination of funding sources (Anderson 1998; Blazar 2006; Cerchietti 2006; Dodd 1996; Ferretti 1988; Foote 1994; Makkonen 1994; Sornsuvit 2008; van der Lelie 2001). Five studies were funded by charities (Bjarnason 2009; Dickson 2000; Franzen 1995; Lilleby 2006; Lockhart 2005). Four trials reported that they received university funding (Biswal 2003; Madan 2008; Motallebnejad 2008; Yuen 2001). Three studies were funded by other sources (Gori 2007; Lin 2006; Oberbaum 2001). The remaining 50 (38%) studies reported either none, or insufficient information about funding sources. A dentist was involved in 26 (20%) of the trials.

Studies awaiting assessment

Due to changes in the inclusion criteria for studies in this review, some previously excluded studies are being reconsidered for inclusion in the next update. Information about these studies is in Characteristics of studies awaiting classification.

Characteristics of the participants

One hundred and fourteen (87%) of the included trials recruited only adult patients, 13 included both adults and children (with a difference in age as large as 1 to 70 years) and three trials were conducted solely on paediatric patients (Cruz 2007; Gandemer 2007; Shenep 1988), the age group being unclear in one trial (Mahood 1991). The type of cancer for which patients were being treated was exclusively head and neck cancer in 69 trials (53%), leukaemia in 13 trials, solid tumours in 22 trials and a combination of haematological and solid tumours in 21 trials, the cancer type being unclear in six 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. Twenty-nine trials included patients who were undergoing a bone marrow transplant. The chemotherapy regimen included 5-fluorouracil (5-FU) in 25 trials. In 13 of these trials the patients had solid tumours, in six trials patients had head and neck cancer, in two trials patients had mixed cancers and in four trials the cancer type was unclear. 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 to 74 Gy and the Karnofsky performance > 60.

Characteristics of the interventions

All of the 131 trials provided a clear description of the interventions including the dose and method of administration for the test and control groups. The dosage of the test agents varied for similar products. Thirty-six trials compared an active intervention with no treatment and 87 trials used a placebo control. In some trials the placebo was matched in taste and appearance to the active intervention and in others the following interventions were described as placebo: water, albumin, glycine, sugar solution, polycal, saline. Two trials included in the no treatment control group tested different oral care protocols and in each case one group received limited oral hygiene (usual care) (Borowski 1994; Shieh 1997). A further three trials included in the placebo control group included both a placebo control and a direct comparison (Freytes 2004 - two different doses of keratinocyte growth factor, Madan 2008 - chlorhexidine versus povidone iodine versus salt & soda, and Sorensen 2008 chlorhexidine mouthwash versus ice chips).
A further two trials (Huang 2003; Wang 2002) compared Chinese medicine to a control described as Dobell's solution, which is "a solution of sodium borate, sodium bicarbonate, phenol, and glycerol, used as a wash for mucous membranes" (Merck Index 2010). Two trials compared patients receiving radiotherapy in the morning with patients receiving radiotherapy in the afternoon (Bjarnason 2009; Goyal 2009). Another four trials compared two active interventions: ice chips sucked for different time periods (30 minutes versus 60 minutes) (Rocke 1993), granulocyte/macrophage colony-stimulating factor (GM-CSF) versus sucralfate (Saarilahti 2002), chlorhexidine versus laser (Arun Maiya 2006) and polaprezinc versus azulene (Watanabe 2010).
The interventions for the 131 studies assessing oral mucositis were:

- aciclovir (Bubley 1989)
- allopurinol mouthrinse (Abbasi-Nazari 2007; Dozono 1989; Loprinzi 1990; Panahi 2009)
- aloe vera (Puataweepong 2009; Su 2004;)

- amifostine (Antonadou 2002; Bourhis 2000; Brizel 2000; Buentzel 2006; Buntzel 1998; Haddad 2009; Hartmann 2001; Koukourakis 2000; Spencer 2005; Vacha 2003; Veerasarn 2006)
- antibiotic pastille or paste (El Sayed 2002)
- antibiotic systemic (clarithromycin) (Yuen 2001)
- azulene (Watanabe 2010*)
- benzydamine (Epstein 1989; Epstein 2001; Kazemian 2009; Prada 1987)
- beta carotene (Mills 1988)
- chamomile (Fidler 1996)
- chewing gum (Gandemer 2007)
- Chinese herbs (details of herbs used are given in Characteristics of included studies table) (Huang 2003*; Wang 2002*)
- chlorhexidine (Arun Maiya 2006*; Dodd 1996; Ferretti 1988; Foote 1994; Madan 2008*; McGaw 1985; Pitten 2003; Sorensen 2008; Spijkervet 1989; Wahlin 1989)
- cryotherapy (Cascinu 1994; Gori 2007; Lilleby 2006; Mahood 1991; Rocke 1993*; Svanberg 2007; Sorensen 2008*)
- dental stent (Qin 2007)
- epidermal growth factor (Wu 2009)
- glutamine (Anderson 1998; Cerchietti 2006; Choi 2007; Dickson 2000; He 2008; Huang 2000; Jebb 1994; Li 2006; Okuno 1999; Sornsuvit 2008)
- granulocyte colony-stimulating factor (G-CSF) (Crawford 1999; Katano 1995; Schneider 1999; Su 2006)
- granulocyte/macrophage colony-stimulating factor (GM-CSF) (Cartee 1995; Chi 1995; Dazzi 2003; Ifrah 1999; Makkonen 2000; McAleese 2006; Nemunaitis 1995; Saarilahti 2002*; van der Lelie 2001)
- histamine gel (Elad 2006)
- honey (Biswal 2003; Motallebnejad 2008; Rashad 2008)
- hydrolytic enzymes (details of enzymes used are given in Characteristics of included studies table) (Dorr 2007; Gujral 2001; Kaul 1999)
- indigo wood root (You 2009)
- intestinal trefoil factor (Peterson 2009)
- iseganan (Giles 2004; Trotti 2004)
- keratinocyte growth factor (GF) (Blazar 2006; Brizel 2008; Freytes 2004*; Meropol 2003; Rosen 2006; Spielberger 2004; Vadhan-Raj 2010)
- laser (Antunes 2007; Arun Maiya 2006*; Bensadoun 1999; Chor 2010; Cruz 2007; Schubert 2007)
- non-steroidal anti-inflammatory drug (Pillsbury 1986)
- oral care (Borowski 1994; Shieh 1997)
- pentoxifylline (Attal 1993)
- pilocarpine (Lockhart 2005; Scarantino 2006)
- PTA (polymixin/tobramycin/amphotericin) lozenges/paste (Stokman 2003; Symonds 1996; Wijers 2001)
- polaprezinc (Watanabe 2010*)
- povidone iodine (Arun Maiya 2006; Madan 2008*; Rahn 1997; Vokurka 2005)
- prednisone (Leborgne 1997)
- propantheline anticholinergic (Ahmed 1993)
- prostaglandin (Duenas 1996; Hanson 1995; Labar 1993; Pillsbury 1986; Veness 2006)
- radiation: morning versus evening (Bjarnason 2009*, Goyal 2009*)
- shenqi-fanghou (Hu 2005)
- superoxide dismutase (SOD) (Tu 1998)
- sucralfate (Carter 1999; Castagna 2001; Cengiz 1999; Epstein 1994; Evensen 2001; Franzen 1995; Lievens 1998; Makkonen 1994; Nottage 2003; Pfeiffer 1990; Saarilahti 2002*; Scherlacher 1990; Shenep 1988)
- traumeel (Oberbaum 2001)
- yangygin-humo decoctalion (Dai 2009)
- zinc sulphate (Ertekin 2004; Lin 2006).

* studies with two or more different active treatments.

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 World Health Organization (WHO) or European Organization for Research and Treatment of Cancer (EORTC). Scales were similar to the 5-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. The duration of the trials varied from a few days up to 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 mm^3. 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.

Secondary outcomes

There was little consistency on the other outcome measures reported.

- Oral hygiene measures (Biswal 2003; Cruz 2007; Dodd 1996; El Sayed 2002; Elad 2006; Ertekin 2004; Evensen 2001; Ferretti 1988; Foote 1994; Gandemer 2007; Kazemian 2009; Leborgne 1997; Lockhart 2005; Makkonen 1994; Makkonen 2000; McGaw 1985; Rahn 1997; Rashad 2008; Scherlacher 1990; Spijkervet 1989; Stokman 2003; Symonds 1996; Vadhan-Raj 2010; Vokurka 2005; Wahlin 1989; Wijers 2001; Wu 2009).
- Relief of pain/use of analgesia (morphine) (Antunes 2007; Arun Maiya 2006; Attal 1993; Bensadoun 1999; Blazar 2006; Brizel 2008; Carter 1999; Castagna 2001; Cengiz 1999; Cerchietti 2006; Cruz 2007; Dazzi 2003; Dorr 2007; El Sayed 2002; Epstein 1989; Epstein 1994; Epstein 2001; Ertekin 2004;

Ferretti 1988; Franzen 1995; Freytes 2004; Gandemer 2007; Giles 2004; Hanson 1995; Lilleby 2006; Lockhart 2005; Makkonen 2000; Meropol 2003; Nottage 2003; Oberbaum 2001; Peterson 2009; Pfeiffer 1990; Prada 1987; Puataweepong 2009; Rosen 2006; Saarilahti 2002; Schubert 2007; Shenep 1988; Shieh 1997; Spencer 2005; Spielberger 2004; Su 2004; Svanberg 2007; Trotti 2004; Tu 1998; Vadhan-Raj 2010; van der Lelie 2001; Veness 2006; Vokurka 2005; Watanabe 2010; Wijers 2001; Wu 2009).

- Duration or severity of dysphagia (Antonadou 2002; Bensadoun 1999; Bjarnason 2009; Bourhis 2000; Brizel 2008; Buntzel 1998; Castagna 2001; Cengiz 1999; Choi 2007; Dorr 2007; El Sayed 2002; Elad 2006; Epstein 1994; Fidler 1996; Franzen 1995; Giles 2004; Goyal 2009; Gujral 2001; Haddad 2009; Hartmann 2001; Kaul 1999; Lievens 1998; Lilleby 2006; Lockhart 2005; McAleese 2006; Oberbaum 2001; Prada 1987; Rosen 2006; Scarantino 2006; Scherlacher 1990; Spielberger 2004; Su 2006; Symonds 1996; Trotti 2004; Vadhan-Raj 2010; Veerasarn 2006; You 2009).
- Use of parenteral nutrition or feeding tube (Bjarnason 2009; Bourhis 2000; Brizel 2008; Carter 1999; Cerchietti 2006; Cruz 2007; Dickson 2000; El Sayed 2002; Evensen 2001; Foote 1994; Franzen 1995; Gandemer 2007; Haddad 2009; Hanson 1995; Hartmann 2001; Leborgne 1997; Lilleby 2006; Lockhart 2005; Rashad 2008; Saarilahti 2002; Shenep 1988; Spencer 2005; Spielberger 2004; Stokman 2003; Su 2006; Symonds 1996; Trotti 2004; Vadhan-Raj 2010; van der Lelie 2001; Yuen 2001).
- Incidence of systemic infection or use of antibiotics (Antunes 2007; Attal 1993; Blazar 2006; Borowski 1994; Brizel 2008; Bubley 1989; Buntzel 1998; Castagna 2001; Cerchietti 2006; Crawford 1999; Cruz 2007; Duenas 1996; El Sayed 2002; Ertekin 2004; Ferretti 1988; Freytes 2004; Gandemer 2007; Hanson 1995; Hartmann 2001; Ifrah 1999; Jebb 1994; Labar 1993; McGaw 1985; Pitten 2003; Puataweepong 2009; Shenep 1988; Sornsuvit 2008; Spencer 2005; Spielberger 2004; Su 2004; Symonds 1996; Trotti 2004; Tu 1998; Vadhan-Raj 2010; van der Lelie 2001; Vokurka 2005; Wahlin 1989; Yuen 2001).
- Febrile episodes (Ahmed 1993; Anderson 1998; Attal 1993; Borowski 1994; Brizel 2000; Chi 1995; Chor 2010; Crawford 1999; Duenas 1996; Ferretti 1988; Freytes 2004; Ifrah 1999; Katano 1995; Labar 1993; McGaw 1985; Nemunaitis 1995; Pitten 2003; Shenep 1988; Spencer 2005; Spielberger 2004; van der Lelie 2001; Vokurka 2005; Wahlin 1989; Yuen 2001).
- Blood changes (Ahmed 1993; Antonadou 2002; Attal 1993; Blazar 2006; Brizel 2000; Buentzel 2006; Buntzel 1998; Cartee 1995; Cascinu 1994; Cerchietti 2006; Chi 1995; Crawford 1999; Dazzi 2003; Dickson 2000; Dorr 2007; Duenas 1996; Elad 2006; Epstein 2001; Ertekin 2004; Ferretti 1988; Franzen 1995; Freytes 2004; Hartmann 2001; Huang 2003; Ifrah 1999; Katano 1995; Labar 1993; Li 2006; Lilleby 2006; Lin 2006; Mahood 1991; Makkonen 2000; Meropol 2003; Nemunaitis 1995; Pitten 2003; Rocke 1993; Rosen 2006; Saarilahti 2002; Schneider 1999; Shenep 1988; Sorensen 2008; Sornsuvit 2008; Spencer 2005; Spielberger 2004; Svanberg 2007; van der Lelie 2001; Veerasarn 2006; Vokurka 2005; Wahlin 1989; Wu 2009; You 2009).
- Treatment interruption (Antonadou 2002; Biswal 2003; Bjarnason 2009; Bourhis 2000; Brizel 2000; Brizel 2008; Carter 1999; Dazzi 2003; El Sayed 2002; Foote 1994; Franzen 1995; Haddad 2009; Huang 2003; Ifrah 1999; Koukourakis 2000; Leborgne 1997; Makkonen 1994; Makkonen 2000; Pfeiffer 1990; Puataweepong 2009; Saarilahti 2002; Trotti 2004; van der Lelie 2001; Vadhan-Raj 2010; Veness 2006; Wu 2009; You 2009).
- Days of stay in hospital (Antonadou 2002; Attal 1993; Cerchietti 2006; Chor 2010; Dickson 2000; Duenas 1996; Ifrah 1999; Lilleby 2006; McGaw 1985; Saarilahti 2002; Sornsuvit 2008; van der Lelie 2001).
- Toxicity - nausea/vomiting/constipation/diarrhoea (Antonadou 2002; Blazar 2006; Bourhis 2000; Brizel 2000; Brizel 2008; Bubley 1989; Buentzel 2006; Cascinu 1994; Castagna 2001; Cengiz 1999; Dickson 2000; Duenas 1996; El Sayed 2002; Elad 2006; Epstein 1994; Epstein 2001; Ertekin 2004; Fidler 1996; Freytes 2004; Gandemer 2007; Giles 2004; Gujral 2001; Haddad 2009; Hartmann 2001; He 2008; Kazemian 2009; Labar 1993; Li 2006; Lievens 1998; Lockhart 2005; Mahood 1991; Meropol 2003; Nottage 2003; Oberbaum 2001; Okuno 1999; Peterson 2009; Pfeiffer 1990; Rocke 1993; Rosen 2006; Scarantino 2006; Shenep 1988; Sornsuvit 2008; Spencer 2005; Trotti 2004; Tu 1998; Vadhan-Raj 2010; Yuen 2001).
- Toxicity - skin changes (Antonadou 2002; Blazar 2006; Bourhis 2000; Buntzel 1998; Choi 2007; Dickson 2000; Dorr 2007; El Sayed 2002; Evensen 2001; Giles 2004; Goyal 2009; Gujral 2001; Haddad 2009; Kaul 1999; Lievens 1998; Lin 2006; Meropol 2003; Rosen 2006; Scarantino 2006; Shenep 1988; Spielberger 2004; Tu 1998; Vacha 2003; Yuen 2001).
- Toxicity - unspecific (Buentzel 2006; Cerchietti 2006; Chi 1995; Duenas 1996; El Sayed 2002; Epstein 1994; Fidler 1996; Freytes 2004; Giles 2004; Gujral 2001; Mahood 1991; Makkonen 1994; Makkonen 2000; Okuno 1999; Puataweepong 2009; Spielberger 2004; Su 2006; Tu 1998).
- Xerostomia (Antonadou 2002; Bourhis 2000; Brizel 2000; Brizel 2008; Buentzel 2006; Buntzel 1998; Castagna 2001; Cengiz 1999; Dazzi 2003; Elad 2006; Epstein 1994; Epstein 2001; Goyal 2009; Hartmann 2001; Koukourakis 2000; Lockhart 2005; Makkonen 2000; McAleese 2006; Meropol 2003; Nottage 2003; Oberbaum 2001; Saarilahti 2002; Scarantino 2006; Spencer 2005; Vacha 2003; Veerasarn 2006; Watanabe 2010).
- Cost (Bourhis 2000; Brizel 2000; Buentzel 2006; Buntzel 1998; Choi 2007; Dodd 1996; Haddad 2009; Hartmann 2001; Hu 2005; Huang 2000; Koukourakis 2000; Makkonen 2000;

McAleese 2006; Nemunaitis 1995; Nottage 2003; Sornsuvit 2008; Su 2006; Yuen 2001).

- Patient quality of life (Bjarnason 2009; Brizel 2000; McAleese 2006; Nottage 2003; Scarantino 2006; Spielberger 2004; Veness 2006).
- Death (Ahmed 1993; Attal 1993; Bjarnason 2009; Blazar 2006; Brizel 2008; Dickson 2000; Dodd 1996; Epstein 2001; Ertekin 2004; Ferretti 1988; Giles 2004; Gujral 2001; Kazemian 2009; Leborgne 1997; Madan 2008; Mills 1988; Oberbaum 2001; Rahn 1997; Rosen 2006; Schubert 2007; Spielberger 2004).
- Weight loss/gain (Antonadou 2002; Biswal 2003; Bjarnason 2009; Brizel 2000; Buentzel 2006; Buntzel 1998; Carter 1999; Cengiz 1999; Cerchietti 2006; El Sayed 2002; Elad 2006; Ertekin 2004; Foote 1994; Freytes 2004; Haddad 2009; Hanson 1995; He 2008; Hu 2005; Huang 2000; Koukourakis 2000; Leborgne 1997; Lievens 1998; Lilleby 2006; Lin 2006; Makkonen 2000; Motallebnejad 2008; Nottage 2003; Pillsbury 1986; Puataweepong 2009; Qin 2007; Shenep 1988; Sornsuvit 2008; Stokman 2003; Su 2004; Su 2006; Symonds 1996; Trotti 2004; Vacha 2003; Veerasarn 2006; Veness 2006; Wu 2009; You 2009).
- Caloric intake by oral nutrition (Castagna 2001; Cruz 2007; Dickson 2000; Freytes 2004; Hartmann 2001; He 2008; Lilleby 2006; Pfeiffer 1990; Shenep 1988; Spencer 2005; Watanabe 2010).
- Eating/drinking difficulty (Anderson 1998; Carter 1999; Cengiz 1999; Cerchietti 2006; Dickson 2000; El Sayed 2002; Evensen 2001; Franzen 1995; Freytes 2004; Jebb 1994; Lilleby 2006; Lockhart 2005; Nottage 2003; Oberbaum 2001; Pfeiffer 1990; Prada 1987; Rashad 2008; Rosen 2006; Scarantino 2006; Shenep 1988; Sornsuvit 2008; Spielberger 2004; Stokman 2003; Symonds 1996; Vadhan-Raj 2010).
- Overall health (Antonadou 2002; Bourhis 2000; Brizel 2000; Buentzel 2006; Elad 2006; Ertekin 2004; Haddad 2009; Ifrah 1999; Jebb 1994; Lilleby 2006; Makkonen 2000; McAleese 2006; Nemunaitis 1995; Rosen 2006; Shenep 1988; Su 2004; Su 2006; Wu 2009).
- Recurrence of cancer (Ahmed 1993; Attal 1993; Bjarnason 2009; Blazar 2006; Brizel 2000; Brizel 2008; Cerchietti 2006; Chi 1995; Dickson 2000; Duenas 1996; Goyal 2009; Gujral 2001; Leborgne 1997; Li 2006; Makkonen 2000; Mills 1988; Okuno 1999; Pillsbury 1986; Rosen 2006; Saarilahti 2002; Schneider 1999; Spielberger 2004; Vadhan-Raj 2010; Watanabe 2010).

Risk of bias in included studies

Adequate sequence generation

Twenty-seven studies (21%) were deemed to have adequate sequence generation, and therefore were classified as being at low risk of bias for this domain. Thirteen of these studies employed computer-based sequence generation; while, four studies employed minimization. Four studies did not provide enough information about the randomisation process; however it was the opinion of the assessors that the setting of these trials made adequate randomisation likely. These studies were conducted at the Dana Faber cancer institute (Haddad 2009), the Memorial Sloan Kettering Cancer Centre (Su 2004), the Duke Centre (Cartee 1995) and the Finish cancer registry (Makkonen 2000). One study used biased coin randomisation (Su 2004). Of the remaining five studies, three used a table of random numbers (Huang 2003; Koukourakis 2000; Pitten 2003), and two studies provided limited information but made reference to appropriate literature concerning randomisation (Brizel 2000; Shieh 1997). Those studies considered to use an inappropriate method of randomisation were excluded; therefore no studies were given a decision of no for this category. The remaining 104 studies (79%) were judged as 'unclear'. The majority of these unclear studies gave no more information than that they were 'randomised'. Four studies stated that they employed the "closed envelope" method of randomisation. However, no information was provided about whether these envelopes were shuffled prior to the patient being randomised. They were therefore classified as "unclear".

Adequate allocation concealment

Nineteen studies (14%) employed adequate methods of allocation concealment and were therefore classified as being at low risk of bias. Central randomisation was mentioned in 15 studies, with eight studies employing pharmacy controlled randomisation, six studies communicating by telephone, and one study by fax (Gandemer 2007). Two studies employed sequentially numbered drug containers which were identical in appearance (Foote 1994; Madan 2008). Two studies (1.5%) used open number tables without concealment and were therefore deemed to be at high risk of bias (Huang 2003; Koukourakis 2000). The remaining 111 studies were classified as unclear.

Blinding

Blinding was assessed for three different groups: patients, carers and outcome assessors.

Carer blinding: Nineteen studies (15%) described some method of blinding and were therefore deemed to be at low risk of bias for carer blinding. Forty-five studies (34%) were classified as being at high risk of bias, as no blinding was employed. Sixty-seven (51%) studies were classified as 'unclear'.

Patient blinding: Forty-five studies were classified as being at high risk of bias for patient blinding. The majority of these were studies which employed no blinding, however one study was described by

its authors as double blind, but then went on to state that a patient withdrew from the study because they were not allocated the intervention of interest (Wu 2009). The assessors were concerned that this suggested a failure in the blinding of patients in this study, and therefore decided to characterise the study at high risk of bias for all three blinding categories. Seventy-five studies (58%) were deemed to be at low risk of bias for patient blinding. Eleven studies (8%) were classified as unclear. Of these studies, four were deemed unclear as they employed the use of a placebo control, and therefore blinding could not be discounted, while three studies were assessed for risk of bias from a data collection sheet provided by a translator without any additional information. Of the remaining four 'unclear' studies, one study which compared povidone-iodine to saline was described as 'blind' to patients, however, this was considered by the assessors to be an inappropriate control as presumably the iodine solution would differ in colour from the saline (Vokurka 2005). Another which investigated zinc in head and neck patients receiving a mix of radiotherapy and chemoradiotherapy (Ertekin 2004), was classified as unclear for two reasons: firstly, because the study authors described the need for a double blind study in the introduction, and then failed to provide any information about blinding in the remainder of the text, and secondly, because the authors used empty capsules as the control, and the assessors were concerned that this would be noticeable to the patients. The third study (Vadhan-Raj 2010) was deemed unclear because the authors stated that adverse events associated with the intervention (keratinocyte growth factor) may have affected the integrity of the blinding. The remaining trial (Ahmed 1993) only stated that "trial drugs were administered blind", without any additional information.

Outcome assessor blinding: Seventy-seven studies (59%) were deemed to describe any method of outcome assessor blinding adequately and were considered to be at low risk of bias. Sixteen studies (12%) were classified as unclear and 38 studies (29%) were given a decision of 'no' and were therefore considered to be at high risk of bias in this category. In a subanalysis of those studies providing blinding information, only 19 studies gave specific information regarding the blinding of an outcome assessor. The remaining 58 studies were only described as "double blind" by the authors.

Incomplete outcome data addressed

One hundred and six studies (82%) were considered to be at low risk of bias for this category. Seventeen studies (13%) were given a decision of unclear and eight were considered to be at high risk of bias. These seven studies experienced a high rate of drop out.

Free of selective reporting

Forty-nine (37%) studies were deemed to be free of selective reporting for mucositis grade, which was determined prior to assessment as the outcome of interest for this category. These studies were therefore deemed to be at a low risk of bias. The remaining 82 studies were classified as unclear. These studies tended to only provide subsets of data for severe mucositis (grade > 2) rather than all the information of interest. No studies were given a decision of 'no', and consequently classified at high risk of bias, as studies which did not provide mucositis information for at least one of the dichotomies of interest could not be included in the review.

Free of other bias

Thirty-five studies (27%) were deemed to be at high risk of bias in the final 'other' category. A baseline imbalance was reported by 11 studies. Three studies reported gender imbalances (Abbasi-Nazari 2007; Makkonen 1994; Puataweepong 2009), while three studies reported age imbalances (Bensadoun 1999; Ifrah 1999; Makkonen 1994). Two or more baseline imbalances were reported by four studies (Bensadoun 1999; Ifrah 1999; Makkonen 1994; Puataweepong 2009). Puataweepong 2009 reported baseline imbalances in both patient gender (P = 0.03) and previous surgery (P = 0.04). Meanwhile, in the Ifrah 1999 study, patients randomised to receive GM-CSF in the intervention arm of the study, were older (P = 0.04) and more likely to have the Philadelphia chromosomal re-arrangement (P = 0.026). Baseline imbalances in age and gender were reported by Makkonen and colleagues (Makkonen 1994). Bensadoun and colleagues reported imbalances in the number of patients receiving supplementary application of laser to the neck, which was hypothesised to exert a distant beneficial effect. In this study patients in the intervention group also tended to be older. However, no P values were presented by the authors for this imbalance (Bensadoun 1999). Risk of bias was assessed for eight studies from a data collection form completed by a translator. Loprinzi and colleagues initially aimed to recruit 120 patients into their allopurinol study, however, the power calculation was re-run after 77 patients and as the results were found to favour the intervention, the study was terminated and the data published (Loprinzi 1990). In the Duenas and colleagues study (Duenas 1996), an interim analysis conducted in the 16 patients recruited into the study showed a significant different in favour of the placebo, and the authors therefore decided to cease recruitment. Epstein and colleagues also report the results of an interim analysis, in this case a trial of 33 patients which compared sucralfate to placebo. This trial was terminated after an interim analysis suggested that the impact of sucralfate on mucositis prevention was minimal (Epstein 1994).

Overall risk of bias

Figure 1; Figure 2.

Eleven studies were assessed at low overall risk of bias (8%) (Cartee 1995; Dazzi 2003; Foote 1994; Madan 2008; Oberbaum 2001; Pitten 2003; Saarilahti 2002; Schneider 1999; Shenep 1988; Stokman 2003; Su 2006), 82 (63%) were described as unclear and the remaining 38 studies (29%) were defined as being at high

overall risk of bias (Antonadou 2002; Antunes 2007; Biswal 2003; Bjarnason 2009; Borowski 1994; Bourhis 2000; Brizel 2000; Buntzel 1998; Cascinu 1994; Chi 1995; Choi 2007; Dai 2009; Dozono 1989; Gandemer 2007; Gori 2007; Gujral 2001; Haddad 2009; Hartmann 2001; Huang 2000; Katano 1995; Kaul 1999; Koukourakis 2000; Lilleby 2006; Makkonen 2000; Mills 1988; Rahn 1997; Rashad 2008; Rocke 1993; Shieh 1997; Spencer 2005; Svanberg 2007; Vacha 2003; Vadhan-Raj 2010; Veerasarn 2006; Wahlin 1989; Watanabe 2010; Wu 2009; Yuen 2001).

Figure 1. Risk of bias assessment graph: review authors' judgements about each risk of bias domain presented as percentages across all included studies.

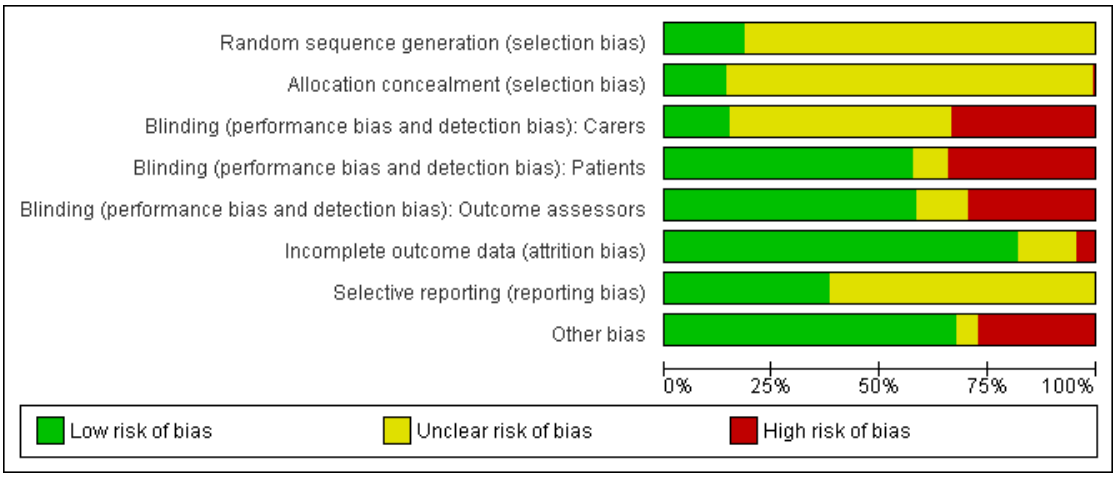
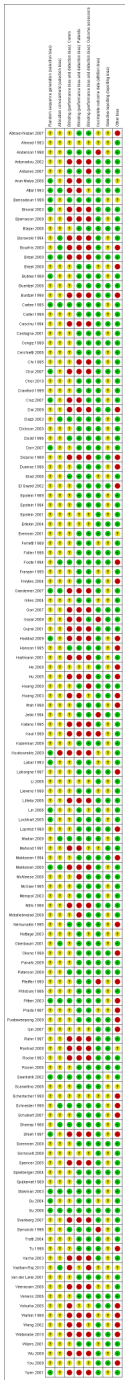


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias domain for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Cryotherapy versus no treatment for preventing oral mucositis for patients with cancer receiving treatment; **Summary of findings 2** Amifostine versus placebo/no treatment for preventing oral mucositis for patients with cancer receiving treatment; **Summary of findings 3** Keratinocyte GF versus placebo for preventing oral mucositis for patients with cancer receiving treatment; **Summary of findings 4** Sucralfate versus placebo/usual care for preventing oral mucositis for patients with cancer receiving treatment; **Summary of findings 5** Chlorhexidine versus placebo/no treatment for preventing oral mucositis for patients with cancer receiving treatment

Interventions with more than one trial

Allopurinol versus placebo/no treatment (Analysis 1.1; Analysis 1.2; Analysis 1.3)

There were four trials (Abbasi-Nazari 2007; Dozono 1989; Loprinzi 1990; Panahi 2009), two designed as cross-over studies (Dozono 1989; Loprinzi 1990), which compared allopurinol mouthrinse with placebo or no treatment. Three of these studies were conducted in patients undergoing treatment with chemotherapy for solid tumours. One study was conducted in patients receiving radiotherapy +/- chemotherapy for head and neck cancer (Abbasi-Nazari 2007). Data were provided for all three outcome categories.

All trials provided data for the outcome category of any mucositis, and there was no statistically significant difference between allopurinol and control, risk ratio (RR) 0.77 (95% confidence interval (CI) 0.50 to 1.19, P = 0.24, Analysis 1.1). Two trials, both assessed as being at unclear risk of bias, provided data for the moderate plus severe and severe outcome categories (Abbasi-Nazari 2007; Panahi 2009). There was substantial heterogeneity in both the moderate plus severe meta-analysis (Chi^2 = 8.24, degrees of freedom (df) = 1, P = 0.004, I^2 = 88%, Analysis 1.2) and the severe meta-analysis (Chi^2 = 13.14, df = 1, P = 0.0003, I^2 = 92%, Analysis 1.3), probably due to differences with regard to the type of tumour and cancer treatment in the trials. The effect estimates from these trials are inconsistent; the risk of bias is unclear and there is substantial heterogeneity.

Overall, there is weak inconsistent evidence which is insufficient to indicate a benefit of allopurinol in the prevention of mucositis.

Aloe vera solution versus placebo (Analysis 2.1)

Two trials (Puataweepong 2009; Su 2004), comprising a total of 119 patients with head and neck cancer undergoing radiotherapy or chemoradiotherapy compared aloe vera with placebo. Both trials were found to be at unclear risk of bias. Both provided data for the outcome category of prevention of moderate plus severe mucositis and showed a statistically significant benefit in favour of aloe vera, RR 0.74 (95% CI 0.58 to 0.96, P = 0.02, Analysis 2.1) with moderate heterogeneity (Chi^2 = 2.42, df = 1 (P = 0.12); I^2 = 59%).

Su 2004 found a statistically significant reduction in severe mucositis in the aloe vera group but Puataweepong 2009 found no difference between the groups with regard to the prevention of any mucositis (Additional Table 1).

Overall, there is weak unreliable evidence that aloe vera may be beneficial in the prevention of moderate to severe mucositis.

Amifostine versus placebo/no treatment (Analysis 3.1; Analysis 3.2; Analysis 3.3)

Eleven trials compared amifostine with no treatment (Antonadou 2002; Bourhis 2000; Brizel 2000; Buntzel 1998; Haddad 2009; Hartmann 2001; Koukourakis 2000; Spencer 2005; Vacha 2003; Veerasarn 2006) or a placebo (Buentzel 2006). Most of the trials recruited adults with head and neck cancer being treated with radiotherapy (Bourhis 2000; Brizel 2000; Veerasarn 2006) or chemoradiotherapy (Antonadou 2002; Buentzel 2006; Buntzel 1998; Haddad 2009; Vacha 2003). Two trials (Hartmann 2001; Spencer 2005) included patients having bone marrow transplants, and one trial (Koukourakis 2000) included adults with solid tumours receiving radiotherapy. Eight trials were found to be at high risk of bias (Antonadou 2002; Bourhis 2000; Brizel 2000; Haddad 2009; Koukourakis 2000; Spencer 2005; Vacha 2003; Veerasarn 2006) and three trials were found to be at unclear risk of bias (Buentzel 2006; Buntzel 1998; Hartmann 2001).

Three trials provided data for the outcome of any mucositis. There was a significant but small benefit for amifostine preventing mucositis in this outcome category with RR = 0.95 (95% CI 0.91 to 0.99, P = 0.007, Analysis 3.1).

Six heterogeneous trials provided data for moderate plus severe mucositis demonstrating a benefit for amifostine compared with placebo or no treatment, RR = 0.75 (95% CI 0.58 to 0.96, P = 0.02, Analysis 3.2). However, this meta-analysis showed substantial heterogeneity: Chi^2 = 25.86, df = 5, P < 0.0001, I^2 = 81%, which is not explained by cancer treatment (radiotherapy or chemotherapy) or dose of amifostine.

Nine trials provided data for severe mucositis and the pooled meta-analysis showed weak evidence of a possible benefit for amifostine in the prevention of severe mucositis, RR = 0.68 (95% CI 0.45 to 1.03, P = 0.07, Analysis 3.3).

A further trial (Vacha 2003) at high risk of bias provided a graph of weekly mean mucositis scores and the text indicated that there

was a statistically significant difference in favour of amifostine compared to no treatment at 2 weeks, however no overall result was given in this paper (Additional Table 2).
The results from these 11 studies indicate that there is weak unreliable evidence that amifostine may prevent oral mucositis in adults.

Benzydamine versus placebo

Four studies compared benzydamine mouthwash (marketed as Difflam®) with placebo, in a combined total of 332 patients. Kazemian 2009 found a statistically significant reduction in severe mucositis and Prada 1987 found a statistically significant reduction in the development of any mucositis associated with benzydamine (Additional Table 1). Both studies were assessed as being at unclear risk of bias.
Two further studies (Epstein 1989; Epstein 2001), both assessed as being at unclear risk of bias, compared benzydamine with placebo and used other mucositis indices to evaluate the outcome. Both trials reported statistically significant differences in favour of benzydamine (Additional Table 2).
There is weak unreliable evidence that the use of benzydamine may reduce the development of mucositis.

Chlorhexidine versus placebo/no treatment (Analysis 4.1; Analysis 4.2; Analysis 4.3)

Nine trials, with a total of 692 participants, compared chlorhexidine mouthwash with either a placebo or no treatment control group. Four trials (Dodd 1996; Ferretti 1988; Foote 1994; Sorensen 2008) provided data for the first outcome category (any mucositis), three trials (Foote 1994; Pitten 2003; Sorensen 2008) provided data for the second outcome level, moderate plus severe mucositis, and four trials (Foote 1994; Sorensen 2008; Spijkervet 1989; Wahlin 1989) provided data for severe mucositis (grade 3 or greater).
Madan 2008 compared three active treatments: chlorhexidine, povidone iodine, and salt/soda mouthwashes with placebo, and McGaw 1985 compared chlorhexidine mouthwash with placebo, and both these studies presented data as mean mucositis scores for each group (Additional Table 1).
Three studies were found to be at low risk of bias (Foote 1994; Pitten 2003; Madan 2008), one study was found to be at high risk of bias (Wahlin 1989). The remaining five studies were found to be at unclear risk of bias (Dodd 1996; Ferretti 1988; McGaw 1985; Sorensen 2008; Spijkervet 1989).
There was substantial heterogeneity in the meta-analysis of any mucositis (Chi^2 = 30.49, df = 3, P < 0.00001, I^2 = 90%, Analysis 4.1) and moderate plus severe (Chi^2 = 10.84, df = 2, P = 0.004, I^2 = 82%, Analysis 4.2) mucositis levels which may be partly due to clinical differences between the studies in terms of the cancer type and treatment. In one trial (Foote 1994) patients received radiotherapy for head and neck cancer, in three trials (Dodd 1996; Pitten 2003; Sorensen 2008) patients received chemotherapy for either solid tumours or mixed cancers and in the fifth study (Ferretti 1988) patients were undergoing chemotherapy conditioning prior to bone marrow transplant.
There was no evidence that chlorhexidine was more effective than placebo or no treatment for any of the outcomes evaluated (Analysis 4.1; Analysis 4.2; Analysis 4.3).
Two further trials (Madan 2008; McGaw 1985) at low and unclear risk of bias respectively, reported statistically significant differences in mean mucositis scores in each group which favoured chlorhexidine over placebo (Additional Table 2).
Overall, there is no evidence of a benefit for chlorhexidine compared with placebo or no treatment, for the prevention of mucositis.

Cryotherapy (ice chips) versus no treatment (Analysis 5.1; Analysis 5.2; Analysis 5.3)

Six trials (Cascinu 1994; Gori 2007; Lilleby 2006; Mahood 1991; Sorensen 2008; Svanberg 2007) compared cryotherapy (ice chips) with either no treatment or placebo (saline) control. Five trials used a parallel group design and one (Mahood 1991) was a cross-over trial. Three of these studies investigated the use of cryotherapy in patients receiving chemotherapy with 5-FU (Cascinu 1994; Mahood 1991; Sorensen 2008); participants in the trial by Gori 2007 received methotrexate, in Lilleby 2006 they were receiving melphalan conditioning in preparation for stem cell transplantation, and in Svanberg 2007 patients received either chemotherapy or total body irradiation prior to bone marrow or stem cell transplantation. Four of these studies were found to be at high risk of bias, and two studies was found to be at unclear risk of bias (Mahood 1991; Sorensen 2008). Five trials presented data in a format suitable for inclusion in meta-analysis.
There was evidence of a benefit associated with the use of ice chips for each of the three outcome categories of mucositis, with RRs of 0.74 (95% CI 0.57 to 0.95, P = 0.02, Analysis 5.1), 0.53 (95% CI 0.31 to 0.91, P = 0.02, Analysis 5.2) and 0.36 (95% CI 0.17 to 0.77, P = 0.008, Analysis 5.3) respectively. However, substantial heterogeneity, likely to be related to the diversity of clinical conditions and treatments, was also identified in each meta-analysis: Chi^2 = 14.77, df = 4, P = 0.005, I^2 = 73% for any mucositis (Analysis 5.1), Chi^2 = 19.02, df = 4, P = 0.0008, I^2 = 79% for moderate plus severe (Analysis 5.2), and Chi^2 = 14.31, df = 4, P = 0.006, I^2 = 72% for the severe outcome category (Analysis 5.3).
The trial by Svanberg 2007 also found that cryotherapy reduced the development of mucositis and oral pain requiring treatment with opioids (Additional Table 2).
Overall, these six heterogeneous trials provide some evidence, with substantial risk of bias, that ice chips are effective in preventing or reducing the severity of mucositis in patients receiving chemotherapy and/or radiotherapy.

Glutamine versus placebo/usual care (Analysis 6.1; Analysis 6.2; Analysis 6.3)

Ten trials (Anderson 1998; Cerchietti 2006; Choi 2007; Dickson 2000; He 2008; Huang 2000; Jebb 1994; Li 2006; Okuno 1999; Sornsuvit 2008) evaluating 433 patients compared the use of glutamine with either a placebo (nine trials) or best supportive care (Choi 2007). Two of these trials were designed as cross-over studies (Anderson 1998; Jebb 1994) and both had data from more than 40% of randomised participants missing from the outcome evaluation. The remaining eight trials used a parallel group design. The smallest trial evaluated only 13 patients (Anderson 1998) and the largest evaluated 124 patients (Okuno 1999). Three trials were conducted in the USA (Anderson 1998; Dickson 2000; Okuno 1999), two in China (He 2008; Li 2006), and one each in Argentina (Cerchietti 2006), Korea (Choi 2007), Taiwan (Huang 2000), Thailand (Sornsuvit 2008), and the UK (Jebb 1994). Two trials were conducted in head and neck cancers undergoing radiation (Huang 2000) or chemoradiation (Cerchietti 2006). Five studies were conducted in patients with solid cancers receiving radiotherapy (Anderson 1998; Choi 2007; He 2008; Jebb 1994; Li 2006). The remaining three studies were conducted in patients with cancers of the blood receiving chemotherapy (Sornsuvit 2008), a group of patients with mixed cancers receiving a mix of radiotherapy and chemotherapy (Dickson 2000) and a group of patients, with unclear cancer type, receiving chemotherapy.

Three trials used a glutamine suspension and instructed patients to either swish it around the mouth and swallow, twice daily (Anderson 1998; Okuno 1999) or swish and then expectorate (Huang 2000). A further four trials compared oral supplementation with 30 grams of glutamine daily (Choi 2007; Dickson 2000; Li 2006) or 15 grams per day (Jebb 1994).

For all three levels of mucositis prevention (any mucositis, moderate to severe or severe), there was no evidence that oral glutamine was different from placebo in the groups of five studies which reported each level of mucositis (RR = 0.78, 95% CI 0.57 to 1.08, P = 0.13, Analysis 6.1; RR = 0.88, 95% CI 0.69 to 1.12, P = 0.31, Analysis 6.2; and RR = 0.69, 95% CI 0.37 to 1.29, P = 0.24, Analysis 6.3 respectively. There was substantial heterogeneity between these studies, in part due to the lower dose in two studies (Jebb 1994 15 g/day, Huang 2000 swish and expectorate) and the lack of a placebo control in another study which was assessed as being at high risk of bias (Choi 2007). The risk of bias was assessed as high in Huang 2000 and unclear in the other five studies, but it should be noted that both the cross-over studies (Anderson 1998; Jebb 1994) had in excess of 40% loss to follow-up.

The remaining three studies compared intravenous (IV) glutamine supplementation with placebo using approximately 30 grams/day (Cerchietti 2006; Sornsuvit 2008) or 20 grams/day added to parenteral nutrition (He 2008). These trials were small (16 to 48 participants) and all are assessed as being at unclear risk of bias. Only one trial reported the prevention of any grade of mucositis or moderate to severe mucositis and found no difference between glutamine and placebo (Sornsuvit 2008). All three trials (including a total of 93 participants) reported the outcome of prevention of severe mucositis, and found a statistically significant 75% decrease in severe mucositis associated with IV glutamine supplementation (RR = 0.25, 95% CI 0.10 to 0.62, P = 0.002, Analysis 6.3). This result should be interpreted with caution as it is based on small numbers of participants in studies at unclear risk of bias.

Overall, there is no evidence of a benefit for oral glutamine supplementation in the prevention of mucositis but there is weak evidence, from small trials at unclear risk of bias, that intravenous glutamine supplementation may be beneficial for the prevention of severe mucositis.

G-CSF (Analysis 7.1; Analysis 7.2)

Three trials, ranging in size from 14 to 195 patients, compared granulocyte colony-stimulating factor (G-CSF) with placebo (Crawford 1999; Schneider 1999; Su 2006) (total n = 249) and one compared G-CSF with no treatment (Katano 1995) (n = 14), for the prevention of mucositis associated with chemotherapy (Crawford 1999; Katano 1995) for solid tumours, or chemoradiotherapy (Schneider 1999) or radiotherapy (Su 2006) for head and neck cancers. Of the four studies in this group, Crawford 1999 has unclear risk of bias, Katano 1995 has high risk of bias, and both Su 2006 and Schneider 1999 were found to be at low risk of bias. However, the data presented in the Schneider 1999 paper are from an interim analysis after the trial was stopped early for reasons that are unclear. In Analysis 7.1 two trials show a benefit associated with G-CSF in the prevention of any mucositis and two do not. As well as substantial clinical heterogeneity with regard to the primary tumours and cancer treatments, there is a very high level of statistical heterogeneity (Chi^2 = 20.48, df = 3, P = 0.0001, I^2 = 85%) among these four trials such that combining the results by meta-analysis is not appropriate. There was a statistically significant reduction in the incidence of severe mucositis in the G-CSF groups compared to placebo (RR 0.36, 95% CI 0.15 to 0.86, P = 0.02, Analysis 7.2) in two homogenous trials (Schneider 1999; Su 2006). However, Su 2006 found no statistically significant difference between G-CSF and placebo in the prevention of moderate plus severe mucositis.

Overall there is weak evidence that G-CSF may be beneficial in the prevention of severe mucositis in patients with head and neck cancer undergoing radiotherapy.

GM-CSF versus placebo/no treatment (Analysis 8.1; Analysis 8.2; Analysis 8.3)

Eight trials compared granulocyte/macrophage colony-stimulating factor (GM-CSF) with a placebo or no treatment control group. Five trials were placebo controlled (Cartee 1995; Dazzi 2003; Ifrah 1999; Nemunaitis 1995; van der Lelie 2001) and three trials had a no treatment control group (Chi 1995; Makkonen

2000; McAleese 2006). Three studies were conducted in patients receiving chemotherapy (Chi 1995) or radiotherapy for head and neck cancer (Makkonen 2000; McAleese 2006). Two studies were conducted in patients with solid cancers receiving chemotherapy (Cartee 1995; Dazzi 2003). The remaining studies were conducted in patients with a mix of cancers receiving either radiotherapy (van der Lelie 2001) or chemotherapy (Ifrah 1999), or a mix of different therapies (Nemunaitis 1995).

Two trials were found to be at low risk of bias (Cartee 1995; Dazzi 2003), two trials were found to be at high risk of bias (Chi 1995; Makkonen 2000) and the remaining four studies were assessed as being at unclear risk of bias.

Two trials provided data for any mucositis, and moderate to severe mucositis outcome categories, with six trials providing data for the severe mucositis outcome category. There was no statistically significant difference between GM-CSF and control for any of the outcome categories (Analysis 8.1; Analysis 8.2; Analysis 8.3).

In the trial by Makkonen 2000 all patients in both groups developed mucositis and "there was no significant difference in the frequency or degree of radiation-induced mucositis between GM-CSF and the control groups". Chi 1995 reported a cross-over study of 20 patients, assessed as being at high risk of bias, which showed some period effect from the first treatment period to the second. The study reports a statistically significant benefit favouring GM-CSF.

Based on these eight trials of 433 patients there is no evidence that GM-CSF is different from either placebo or no treatment in the prevention of mucositis.

Honey versus no treatment control (Analysis 9.1; Analysis 9.2; Analysis 9.3)

Three trials (Biswal 2003; Motallebnejad 2008; Rashad 2008), each with 40 randomised patients, compared honey with a no treatment control for the prevention of mucositis. In Biswal 2003, 20 patients in Malaysia with head and neck cancer, who were undergoing radiotherapy, smeared honey on their mouth, and then swallowed slowly to coat the mucosa, both prior to and after radiotherapy. Patients in the control group received radiotherapy only. This intervention was replicated some 4 years later in Iran (Motallebnejad 2008) in another group of 40 patients undergoing radiotherapy for head and neck cancer and also in Egypt (Rashad 2008) in a group of patients undergoing chemoradiotherapy for head and neck cancer. In Motallebnejad 2008 outcome assessors were blinded to treatment allocation and risk of bias in this study was assessed as unclear, and in the other two studies there was no blinding or allocation concealment and risk of bias is assessed as high. None of these trials provided any information on compliance with treatment and none recorded any drop outs or losses to follow-up.

There is weak unreliable evidence from these three small trials that honey is associated with a moderate benefit with regard to the prevention of any mucositis (RR 0.70, 85% CI 0.56 to 0.88, P = 0.002), moderate to severe mucositis (RR 0.48, 95% CI 0.31 to 0.74, P = 0.0009) and severe mucositis (RR 0.26, 95% CI 0.13 to 0.52, P = 0.0002). However, in view of the considerable statistical heterogeneity and high risk of bias these results should be interpreted with caution.

Hydrolytic enzymes versus no treatment (Analysis 10.1; Analysis 10.2)

Three trials (Dorr 2007; Gujral 2001; Kaul 1999) compared hydrolytic enzymes with either a placebo (Dorr 2007) or radiotherapy only control, in a total of 210 patients receiving radiotherapy for head and neck cancers. Dorr 2007 was double blind, but overall risk of bias was unclear, and Gujral 2001 and Kaul 1999 were assessed as being at high risk of bias overall.

Two trials reported the outcome category of any mucositis (Gujral 2001; Kaul 1999) with conflicting results (Analysis 10.1) and considerable statistical heterogeneity, so these data were not pooled.

All three trials provided data for the prevention of moderate plus severe mucositis. There was considerable heterogeneity identified so these data were not pooled. The placebo controlled study found no difference between the groups (Dorr 2007) but the other two studies, both at high risk of bias, found a benefit favouring hydrolytic enzymes with radiotherapy compared to radiotherapy alone which was not statistically significant.

The three trials also had some differences with regard to the ingredients in the hydrolytic enzyme intervention. Dorr 2007 and Gujral 2001 used a preparation containing papain 100 mg, trypsin 40 mg and chymotrypsin 40 mg, and Kaul 1999 used a preparation containing papain, trypsin, chymotrypsin, pancreatin, rutin and bromelain.

In summary, the evidence from these three trials is conflicting, and all trials are at some risk of bias. There is insufficient evidence that the use of hydrolytic enzymes to prevent mucositis associated with radiotherapy for head and neck cancers is significantly different from placebo or no treatment.

Iseganan versus placebo (Analysis 11.1; Analysis 11.2)

Two studies (Giles 2004; Trotti 2004), comprising a total of 1013 patients, both at unclear risk of bias, compared iseganan with placebo for different outcome categories of mucositis. One study was conducted in patients with a mix of cancers receiving a range of different cancer treatments (Giles 2004). The other study was conducted in patients with head and neck cancers receiving a mix of cancer therapies (Trotti 2004). These studies provided data for the moderate plus severe and severe outcome categories of mucositis, and both meta-analyses showed no evidence of a difference between iseganan and placebo (Analysis 11.1; Analysis 11.2).

Overall there is no evidence from these trials that iseganan is more or less effective than placebo.

Keratinocyte GF versus placebo (Analysis 12.1; Analysis 12.2; Analysis 12.3)

Seven trials compared keratinocyte growth factor (GF) (marketed as either Palifermin® or Velafermin®) with placebo (Blazar 2006; Brizel 2008; Freytes 2004; Meropol 2003; Rosen 2006; Spielberger 2004; Vadhan-Raj 2010). Six studies were judged to be at unclear risk of bias. One study was judged to be at high risk of bias (Vadhan-Raj 2010). Two provided data for any mucositis, seven for moderate plus severe and six for severe. All three mucositis outcome categories showed evidence of a benefit associated with keratinocyte GF with RR 0.82 (95% CI 0.71 to 0.94, P = 0.005, Analysis 12.1) for any mucositis, RR 0.74 (95% CI 0.62 to 0.89, P = 0.002, Analysis 12.2) for moderate plus severe mucositis and RR 0.72 (95% CI 0.58 to 0.90, P = 0.004, Analysis 12.3) for severe mucositis.

However, there is substantial heterogeneity in the any mucositis (Chi^2 = 10.11, df = 1, P = 0.001, I^2 = 90%, Analysis 12.1) and moderate to severe mucositis outcome categories (Chi^2 = 50.75, df = 6, P < 0.00001, I^2 = 88%, Analysis 12.2). From the table below there is no evidence that this heterogeneity can be explained by differences between the studies in terms of cancer type, cancer treatment, dose or type of keratinocyte GF.

From these seven trials there is some evidence that keratinocyte growth factor is effective in the prevention of mucositis.

Author	Type of keratinocyte	Dose of keratinocyte	Schedule	Number and gender of patients	Cancer type	Treatment
Blazar 2006	Palifermin	40 µg/kg or 60 µg/kg	Cohort 1: patients randomised to placebo or palifermin at either 40 µg (8 patients, total dose 240 µg) or 60 µg (10 patients, total dose 360 µg) per day for 3 days before conditioning (days -11 to -9) and for 3 days after transplant (days 0, 1 and 2) Cohort 2: 14 patients received palifermin at 60 µg/day, for 3 days before conditioning (day -11 to -9) and then for 6 days after transplant (days 0-2 and then days 7-9) (9 doses total). Total dose of palifermin received was 540 µg	100 (58M/ 42F)	Leukaemia, lymphoma, myelodysplastic syndrome	Allogeneic stem cell transplant. Cyclophosphamide 60 mg/kg per day, TBI total dose = 13.2 Gy (fractionated as 165 Gy twice daily for 4 days) or busulfan 1 mg/kg per dose given 4 times daily for 4 days then cyclophosphamide 60 mg/kg per day for 2 days

(*Continued*)

			Cohort 3: 37 patients received palifermin at 60 µg/day for 3 days before conditioning (day -11 to -9) and then for 9 days after transplant (days 0-2, 7-9 and 14-16) (12 doses total). Total dose of palifermin received was 720 µg			
Brizel 2008	Palifermin	60 µg (67 patients)	1 dose administered weekly on the Friday before the first week of chemotherapy (then continued each Friday for 7 consecutive weeks). 2 additional doses given weeks 8 and 9	99 (82M/17F)	Head and neck	Chemotherapy (cisplatin 20 mg/m^2/d IV bolus and fluorouracil 1000 mg/m^2/d continuous infusion) administered for first 4 days of the first and fifth weeks of radiotherapy Radiotherapy (daily fractions of 2 Gy until 70 Gy) or hyperfractionated radiotherapy (1.25 Gy twice daily until 72 Gy)
Freytes 2004	Repifermin	25 µg/kg or 50 µg/kg	Cohort 1: 25 µg/kg repifermin. Cohort 2: 50 µg/kg repifermin	42 (31M/11F)	Haematologic malignancies or lymphoma	Autologous stem cell transplant. Cyclophosphamide, etoposide and carmustine, or melphalan monotherapy, or melphalan combination, or cy-

(*Continued*)

						clophosphamide + TBI or thiotepa + TBI or cyclophosphamide + busulfan
Meropol 2003	Palifermin	1 µg/kg/d or 10 µg/kg/d or 20 µg/kg/d or 40 µg/kg/d or 60 µg/kg/d or 80 µg/kg/d	All cohorts received palifermin on days 1 to 3 of each cycle Cohort 1: 1 µg/kg/d palifermin Cohort 2: 10 µg/kg/d palifermin Cohort 3: 20 µg/kg/d palifermin Cohort 4: 40 µg/kg/d palifermin Cohort 4: 60 µg/kg/d palifermin Cohort 5: 80 µg/kg/d palifermin. 27 placebo patients (randomised 1:1 in cohort 1 and 2:1 in all other cohorts)	81(47M/34F)	Metastatic colorectal cancer	Leucovorin 20 mg/m^2 by IV followed immediately by 425 mg/m^2 for 5 consecutive days on days 4 to 8 of each 28 day cycle
Rosen 2006	Palifermin	40 µg/kg per day (28 patients)	3 consecutive days before chemotherapy	64 (42M/22F)	Solid tumours (colon and rectum)	Chemotherapy (5-FU 425 mg/m^2/day IV for 5 days, leucovorin 20 mg/m^2/day for 5 days)
Spielberger 2004	Palifermin	60 µg/kg per day	3 consecutive days (starting 3 days before TBI) and 3 consecutive doses after transplantation (day 0, day 1, day 2)	212 (131M/81F)	Lymphoma, leukaemia and multiple myeloma	Autologous stem cell transplant. TBI (total 1200 Gy) chemotherapy included etoposide (60 mg/kg) and cyclophosphamide (100 mg/kg)

(*Continued*)

Vadhan-Raj 2010	Palifermin	180 µg/kg	1 dose 3 days before chemotherapy	48 (25M/23F)	Sarcoma	Chemotherapy (doxorubicin 90 mg/m^2 over 72 hours, ifosfamide 10 m/m^2 3 hour infusion for 4 days)

Laser versus placebo or sham control (Analysis 13.1; Analysis 13.2; Analysis 13.3)

Five studies (Antunes 2007; Bensadoun 1999; Chor 2010; Cruz 2007; Schubert 2007), comprising a total of 234 patients, compared laser with a sham laser placebo or no treatment control. Data were provided for all three outcome categories of mucositis. Four of these trials were found to be at unclear risk of bias (Bensadoun 1999; Chor 2010; Cruz 2007; Schubert 2007) and one was assessed to be at high risk of bias (Antunes 2007). Two trials were conducted in patients with a mix of cancers (Antunes 2007; Cruz 2007), one in patients with head and neck cancer undergoing radiotherapy (Bensadoun 1999), one in patients with haematological malignancies undergoing a range of treatments (Schubert 2007) and in the remaining study, the type of cancer and cancer treatment was unclear (Chor 2010).

There was no evidence of a difference in the incidence of any mucositis (RR 0.91, 95% CI 0.71 to 1.17, P = 0.47, Analysis 13.1) or moderate plus severe mucositis (RR 0.64, 95% CI 0.38 to 1.08, P = 0.10, Analysis 13.2) between the laser and control, but there was a statistically significant 80% reduction in the incidence of severe mucositis in the laser group compared to sham or no treatment control (RR 0.20, 95% CI 0.06 to 0.62, P = 0.006, Analysis 13.3).

There was substantial heterogeneity in both the moderate plus severe (Chi^2 = 4.62, df = 1, P < 0.03, I^2 = 78%, Analysis 13.2) and severe outcome categories (Chi^2 = 3.20, df = 1, P = 0.07, I^2 = 69%, Analysis 13.3), which may be partly explained by a variation in the laser wavelengths used in the trials: one trial used a wavelength of 660 nm (Antunes 2007) while the other study used a wavelength of 780 nm (Cruz 2007). In addition, Cruz 2007 recruited children, while Antunes 2007 recruited adults. Both studies were conducted in patients undergoing stem cell transplantation.

The study by Bensadoun 1999 reported the outcome in terms of a mean grade of mucositis in each group over the duration of radiotherapy, and found a statistically significant difference favouring laser (Additional Table 2). Schubert 2007 compared two different lasers (650 nm and 780 nm) with a placebo arm in patients undergoing myeloablative therapy prior to bone marrow transplantation. Mean mucositis scores using the oral mucositis index were reported every 3 days over the 21 day treatment period. "The peak severity of mucositis that generally occurs during the second week of transplant was reduced in the 650 nm laser group" (Additional Table 2).

Overall there is weak evidence from two small studies at some risk of bias that low energy laser application may be beneficial in preventing severe mucositis.

Oral care protocol versus none (Additional Table 1)

Two studies (Borowski 1994; Shieh 1997) compared an intense oral care protocol with none (usual care). Borowski 1994 included 166 patients both adults and children undergoing bone marrow transplantation (study has unclear risk of bias) and Shieh 1997 included 30 adults undergoing radiotherapy for head and neck cancers (study at high risk of bias).

Borowski 1994 found no evidence of a difference between the groups with regard to the prevention of moderate plus severe or severe mucositis, but Shieh 1997 found a statistically significant difference favouring the oral care protocol in the prevention of any mucositis (Additional Table 1).

Based on these two studies there is no evidence that specific oral care protocols are any different from usual care with regard to the prevention of mucositis.

Pilocarpine versus placebo (Analysis 14.1; Analysis 14.2; Additional Table 1)

Two trials, both found to be at unclear risk of bias, compared pilocarpine versus placebo in patients with mixed cancers receiving a range of therapies (Lockhart 2005) and patients with head and neck cancer receiving radiotherapy (Scarantino 2006). The two trials showed inconsistent results and no evidence of benefit was found with regard to the prevention of mucositis for any of the outcome categories (Analysis 14.1; Analysis 14.2; Additional Table 1).

Therefore there is no evidence from these two studies that pilocarpine is more or less effective than placebo in preventing mucositis.

Povidone versus water (Analysis 15.1; Analysis 15.2; Analysis 15.3)

Two trials compared povidone with water or saline (Rahn 1997; Vokurka 2005). One of these studies was found to be at unclear (Vokurka 2005) risk of bias, and the other study was found to be at high risk of bias (Rahn 1997). No statistically significant differences were found for any of the outcome categories (Analysis 15.1; Analysis 15.2; Analysis 15.3).

There is no evidence from these two studies that povidone is more or less effective than placebo in preventing mucositis.

Prostaglandin versus placebo (Analysis 16.1; Analysis 16.2)

Four trials, all found to be at unclear risk of bias, compared prostaglandin with a placebo (Duenas 1996; Hanson 1995; Labar 1993; Veness 2006). Participants (total of 228) had a range of cancers including head and neck (Hanson 1995; Veness 2006), haematological (Labar 1993) and mixed locations (Duenas 1996), treated by radiotherapy, radiotherapy and/or chemotherapy, and chemotherapy respectively. There was no statistically significant difference between prostaglandin and placebo for the prevention of any mucositis (Analysis 16.1), or the prevention of severe mucositis (Analysis 16.2). The trial by Hanson 1995 reported conflicting results for results for the two study centres (Additional Table 1).

There is no evidence from these four trials that prostaglandin is different from placebo in the prevention of mucositis.

PTA antibiotic pastille or paste versus placebo (Analysis 17.1; Analysis 17.2)

Two trials compared antibiotic + antifungal pastilles (containing polymixin, tobramycin and amphotericin (PTA)) with a placebo (Stokman 2003; Symonds 1996) and one trial compared PTA antibiotic paste with a placebo (Wijers 2001). In total 356 patients, all undergoing radiotherapy for head and neck cancers, were included in the trials. Stokman 2003 was assessed as being at low risk of bias and the other two trials at unclear risk of bias.

Two trials provided data for any mucositis (Symonds 1996; Wijers 2001) and the pooled estimate showed evidence of a benefit favouring PTA for the prevention of any mucositis (RR 0.87, 95% CI 0.78 to 0.96, P = 0.008, Analysis 17.1). With regard to the prevention of severe mucositis there was evidence of a difference between PTA and placebo in the two studies that provided data for this outcome (Stokman 2003; Wijers 2001; Analysis 17.2). Likewise there was no statistically significant difference with regard to moderate plus severe mucositis in the only study that provided data for this outcome category (Wijers 2001; Additional Table 1).

In summary there is some weak evidence that the use of PTA applied locally may prevent mucositis in adults with head and neck cancer undergoing radiotherapy, but further high quality trials are required to confirm this.

Radiation: morning versus afternoon (Analysis 18.1)

Two trials (Bjarnason 2009; Goyal 2009), with a total of 428 patients, compared radiotherapy delivered in the morning to administration of radiotherapy in the evening, in patients with head and neck cancers. One of these studies was found to be at high risk of bias (Bjarnason 2009) and the other study was assessed as being at unclear risk of bias (Goyal 2009). No evidence of a difference was found for the prevention of severe mucositis (Analysis 18.1) from the two studies, nor for the prevention of moderate plus severe mucositis in Goyal 2009 (Additional Table 3).

From these two studies there is no evidence that the time of day that radiotherapy treatment is delivered makes a difference with regard to the prevention of mucositis.

Sucralfate versus placebo/usual care (Analysis 19.1; Analysis 19.2; Analysis 19.3)

Twelve parallel group trials evaluated the use of sucralfate; 10 compared sucralfate mouthwash with placebo (Carter 1999; Castagna 2001; Cengiz 1999; Epstein 1994; Franzen 1995; Lievens 1998; Makkonen 1994; Nottage 2003; Pfeiffer 1990; Shenep 1988), and one compared sucralfate mouthwash with usual care (Scherlacher 1990). The remaining trial in this group compared sucralfate mouthwash with placebo, but also instructed all participants to apply sucralfate gel to the skin on one side of the radiation area (resulting in possible contamination of the placebo group) (Evensen 2001). Four trials were conducted in Scandinavia (Evensen 2001; Franzen 1995; Makkonen 1994; Pfeiffer 1990), four in Europe (Castagna 2001; Cengiz 1999; Lievens 1998; Scherlacher 1990), two in the USA (Carter 1999; Shenep 1988), and two in Canada (Epstein 1994; Nottage 2003). Only one of these studies was found to be at low risk of bias (Shenep 1988). All other studies were assessed as being at unclear risk of bias.

Most of the trials recruited participants with head and neck cancer undergoing radiotherapy (Cengiz 1999; Epstein 1994; Evensen 2001; Franzen 1995; Lievens 1998; Makkonen 1994; Scherlacher 1990;) and of the remainder two recruited participants with head and neck cancer undergoing either chemotherapy or combined treatments (Carter 1999; Pfeiffer 1990) and three recruited patients with both a range of cancers and treatment regimens. Patients were instructed to swish the solution in their mouths for 5 minutes, three or four times a day and either swallow the solution or expectorate.

Because the intervention and comparison in Evensen 2001 are unique in this sucralfate group, the results are reported in Additional Table 1. There was no evidence from this study, at unclear

risk of bias, that sucralfate mouthwash plus sucralfate gel applied to the skin is different from sucralfate gel alone in the prevention of mucositis.

There was no evidence of a difference between the sucralfate group and the placebo group in the proportion of patients who developed any mucositis in the three trials, all at unclear risk of bias, that reported this outcome (RR 1.00, 95% CI 0.91 to 1.10, P = 0.93, Analysis 19.1).

However there was some evidence that sucralfate may be beneficial in the prevention of moderate plus severe mucositis in the four trials that reported this outcome (RR 0.75, 95% CI 0.54 to 1.04, P = 0.08, Analysis 19.2). One of these trials was at low risk of bias and the remaining three were assessed as unclear.

Seven trials, one at low and six at unclear risk of bias, provide evidence that sucralfate was effective in the prevention of severe mucositis, with a 33% reduction in severe mucositis in the sucralfate group compared to placebo (RR 0.67, 95% CI 0.48 to 0.92, P = 0.01, Analysis 19.3).

A further two trials (Epstein 1994; Lievens 1998) reported outcome data in a different format, but neither found a statistically significant difference between sucralfate and placebo in the prevention of mucositis (Additional Table 1).

From 9 trials including a total of 516 participants, which compared sucralfate mouthwash with placebo, and provided data for meta-analysis, there is some evidence that sucralfate may prevent moderate plus severe mucositis and stronger evidence of a 33% reduction in severe mucositis.

Zinc sulphate versus placebo

Two trials (Ertekin 2004; Lin 2006) including a total of 127 patients with head and neck cancer undergoing chemotherapy and/or radiotherapy compared oral zinc supplementation with placebo. Both trials were assessed as being at unclear risk of bias.

Ertekin 2004 found no statistically significant difference between zinc supplementation and placebo with regard to the prevention of any mucositis, but a statistically significant difference favouring zinc supplementation in the prevention of moderate plus severe and severe mucositis (Additional Table 1). The other study evaluating this comparison (Lin 2006) presented results in graphs and stated that there was no statistically significant difference between the groups (Additional Table 2).

There is conflicting evidence from these two studies and more research is necessary to determine whether zinc supplementation is better than placebo with regard to the prevention of mucositis.

Comparisons evaluated by a single study

Additional Table 1 presents the data from the comparisons for which there was only one trial evaluating a comparison or only one trial reporting data for one or more of the mucositis outcome categories.

We have summarised the data from the single trials below, indicating where a statistically significant difference is shown (detailed data given in Additional Table 1).

- Aciclovir versus placebo - Bubley 1989: no statistically significant difference for the prevention of any mucositis. Study assessed as being at unclear risk of bias.
- BCoG (bacitracin, cotrimoxazole, gentamicin) antibiotic pastilles - El Sayed 2002: no statistically significant difference between antibiotic and placebo for any of the outcome categories. Study assessed as being at unclear risk of bias.
- Beta carotene versus no treatment control - Mills 1988: no statistically significant difference for severe mucositis. Study assessed as being at high risk of bias.
- Camomile versus placebo - Fidler 1996: no statistically significant difference for all levels of mucositis. Study assessed as being at unclear risk of bias.
- Chewing gum versus no chewing gum - Gandemer 2007: no statistically significant difference for any or severe mucositis. Study assessed as being at high risk of bias.
- Clarithromycin (systemic antibiotic) versus no treatment - Yuen 2001: no statistically significant difference for moderate plus severe mucositis. Study assessed as being at high risk of bias.
- Dental stent versus no treatment control - Qin 2007: no statistically significant difference for moderate plus severe or severe mucositis. Study assessed as being at unclear risk of bias.
- Epidermal growth factor versus placebo - Wu 2009: statistically significant benefit for prevention of moderate plus severe mucositis. Study judged at high risk of bias.
- Histamine gel versus placebo - Elad 2006: no statistically significant difference for any or severe mucositis. Study assessed as being at unclear risk of bias.
- Indomethacin versus placebo - Pillsbury 1986: no statistically significant difference for the prevention of moderate plus severe mucositis. Study assessed as being at unclear risk of bias.
- Indigo wood root versus saline - You 2009: no statistically significant difference for moderate to severe mucositis. Significant benefit for the prevention of severe mucositis. Study assessed as being at unclear risk of bias.
- Intestinal trefoil factor versus placebo - Peterson 2009: statistically significant benefit for prevention of any mucositis and moderate plus severe mucositis, no statistically significant difference for severe only mucositis. Study assessed as being at unclear risk of bias.
- Pentoxifylline versus no treatment - Attal 1993: no statistically significant difference for moderate to severe mucositis. Study assessed as being at unclear risk of bias.
- Prednisone versus placebo - Leborgne 1997: no statistically significant difference for all levels of mucositis. Study assessed as being at unclear risk of bias.
- Propantheline versus placebo - Ahmed 1993: no statistically significant difference for any mucositis. Study assessed as being at

unclear risk of bias.

- Shenqi-fanghou versus no treatment - Hu 2005: statistically significant benefit for the prevention of any, moderate plus severe and severe mucositis. Study assessed as being at unclear risk of bias.
- Superoxide dismutase (SOD) versus placebo - Tu 1998: no statistically significant difference for the prevention of any mucositis. Study assessed as being at unclear risk of bias.
- Traumeel versus placebo - Oberbaum 2001: no statistically significant difference was found for any mucositis. Study assessed as being at low risk of bias.

Comparisons of two active interventions for preventing mucositis

Most of the studies compared an active intervention to either placebo or no treatment. However, two trials (Freytes 2004; Sorensen 2008) had three comparative treatment arms (two active plus placebo) and the results of the direct comparisons are included in Additional Table 3 and summarised below. A further two of these trials (Bjarnason 2009; Goyal 2009) evaluated morning versus afternoon delivery of radiotherapy and the results are described in the section 'Interventions with more than one trial' because both studies used the same interventions. Further details are in Analysis 18.1 and Additional Table 3.

A further seven trials directly compared two active interventions only (Arun Maiya 2006; Dai 2009; Huang 2003; Rocke 1993; Saarilahti 2002; Wang 2002; Watanabe 2010). The data reported in these trials are recorded in Additional Table 3, and the outcomes are summarised in the list below.

- Chinese herbs (mix of six types) versus Dobell's solution (Wang 2002: significant benefit for prevention of any and moderate plus severe mucositis. Study judged at unclear risk of bias).
- Chinese herbs (mix of 11 types) versus Dobell's solution (Huang 2003: significant benefit for the prevention of moderate plus severe and severe mucositis. Study judged at unclear risk of bias).
- Chlorhexidine verus cryotherapy (Sorensen 2008: no statistically significant difference for all levels of mucositis).
- Cryotherapy 30 versus 60 minutes (Rocke 1993: no statistically significant difference for all levels of mucositis).
- GM-CSF versus sucralfate (Saarilahti 2002: no statistically significant difference for moderate plus severe and severe mucositis).
- Keratinocyte growth factor 50 versus 25 mg (Freytes 2004: no statistically significant difference for moderate plus severe and severe only mucositis).
- Laser versus povidone (Arun Maiya 2006: statistically significant for moderate plus severe, and severe only mucositis. Study judged at unclear risk of bias).
- Polaprezinc versus azulene (Watanabe 2010: statistically significant benefit for polaprezinc for moderate plus severe, and severe only mucositis).
- Yangyin humo decoctalion versus 'traditional Western medicine' (Dai 2009: significant benefit for the prevention of moderate plus severe mucositis. Study judged at high risk of bias).

Where there was no statistically significant difference between the interventions compared, it is acknowledged that this could be because the interventions were either equally effective or equally ineffective.

This review proposed to conduct subgroup analyses for different cancer types, cancer treatments and age groups. We were unable to undertake this as there were insufficient numbers of studies in the subgroups. However we did look at whether the heterogeneity was explained by different cancer types or treatments for amifostine and keratinocyte growth factor, by undertaking a sensitivity analysis and this is reported under these interventions in the section above.

We prepared summary of findings tables for those interventions where there was a substantial body of evidence comprising a combined total of at least 550 participants in at least three trials. Selection of interventions to be included in summary of findings tables was not influenced by the results of the trials. Five interventions with a substantial body of evidence were identified. For four interventions there was a substantial body of evidence showing some effectiveness: cryotherapy (Summary of findings for the main comparison), amifostine (Summary of findings 2), keratinocyte growth factor (Summary of findings 3) and sucralfate (Summary of findings 4). The body of evidence concerning chlorhexidine (Summary of findings 5) showed no evidence that chlorhexidine was different from placebo or no treatment in the prevention of mucositis.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Amifostine versus placebo/no treatment for preventing oral mucositis for patients with cancer receiving treatment

Patient or population: preventing oral mucositis for patients with cancer receiving treatment
Settings:
Intervention: Amifostine versus placebo/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Amifostine versus placebo/no treatment				
Mucositis (any) 0-4 scale Follow-up: median 28 days	**Low risk population**[1]		**RR 0.95** (0.91 to 0.99)	430 (3 studies)	⊕⊕⊕○ **moderate**[2]	
	600 per 1000	**570 per 1000** (546 to 594)				
	High risk population[1]					
	950 per 1000	**902 per 1000** (865 to 941)				
Mucositis (severe) 0-4 scale Follow-up: median 28 days	**Low risk population**[3]		**RR 0.68** (0.45 to 1.03)	845 (9 studies)	⊕○○○ **very low**[4,5,6]	
	300 per 1000	**204 per 1000** (135 to 309)				
	High risk population[3]					
	650 per 1000	**442 per 1000** (292 to 669)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Based on the range of absolute risk of developing any mucositis of patients (with different cancer types and treatments) in the control groups of the included studies.
[2] Two trials at high risk of bias and one unclear.
[3] Based on the range of absolute risk of developing severe mucositis of patients (with different cancer types and treatments) in the control groups of included studies.
[4] Six trials at high risk of bias and three unclear.
[5] Substantial heterogeneity, Chi squared 40.39, df=8, P<0..0001, I squared =80% with inconsistency (one trial favouring control)
[6] Wide confidence intervals, small studies and/or low event rates

Keratinocyte GF versus placebo for preventing oral mucositis for patients with cancer receiving treatment

Patient or population: patients with preventing oral mucositis for patients with cancer receiving treatment
Settings:
Intervention: Keratinocyte GF versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Keratinocyte GF versus placebo				
Mucositis (any) 0-4 scale Follow-up: median 28 days	**Low risk population**[1]		**RR 0.82** (0.71 to 0.94)	160 (2 studies)	⊕⊕◯◯ **low**[2,3]	
	600 per 1000	**492 per 1000** (426 to 564)				
	High risk population[1]					
	950 per 1000	**779 per 1000** (674 to 893)				
Mucositis (severe) 0-4 scale Follow-up: median 28 days	**Low risk population**[4]		**RR 0.72** (0.58 to 0.9)	559 (6 studies)	⊕⊕◯◯ **low**[5,6]	
	300 per 1000	**216 per 1000** (174 to 270)				
	High risk population[4]					
	650 per 1000	**468 per 1000** (377 to 585)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Based on the range of absolute risk of developing any mucositis of patients (with different cancer types and treatments) in the control groups of the included studies.
[2] Two studies at unclear risk of bias
[3] Substantial heterogeneity Chi squared =10.11 df=1, P=0.001, I squared =90%.
[4] Based on the range of absolute risk of developing severe mucositis of patients (with different cancer types and treatments) in the control groups of the included studies.
[5] One study at high risk of bias and five at unclear risk of bias.
[6] Moderate heterogeneity Chi squared 10.37, df=5,P=0.07, I squared =52%

Sucralfate versus placebo/usual care for preventing oral mucositis for patients with cancer receiving treatment

Patient or population: preventing oral mucositis for patients with cancer receiving treatment
Settings:
Intervention: Sucralfate versus placebo/usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Sucralfate versus placebo/usual care				
Mucositis (any) 0-4 scale Follow-up: median 28 days	**Low risk population**[1]		**RR 0.98** (0.88 to 1.1)	222 (3 studies)	⊕⊕⊕◯ **moderate**[2]	
	600 per 1000	**588 per 1000** (528 to 660)				
	High risk population[1]					
	950 per 1000	**931 per 1000** (836 to 1000)				
Mucositis (severe) 0-4 scale Follow-up: median 28 days	**Low risk population**[3]		**RR 0.67** (0.48 to 0.92)	428 (7 studies)	⊕⊕⊕◯ **moderate**[4]	
	300 per 1000	**201 per 1000** (144 to 276)				
	High risk population[3]					
	650 per 1000	**435 per 1000** (312 to 598)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Based on the range of absolute risk of developing any mucositis of patients (with different cancer types and treatments) in the control groups of the included studies.
[2] All studies at unclear risk of bias
[3] Based on the range of absolute risk of developing severe mucositis of patients (with different cancer types and treatments) in the control groups of the included studies.
[4] One study at low risk of bias and six at unclear risk of bias

Chlorhexidine versus placebo/no treatment for preventing oral mucositis for patients with cancer receiving treatment

Patient or population: preventing oral mucositis for patients with cancer receiving treatment
Settings:
Intervention: Chlorhexidine versus placebo/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Chlorhexidine versus placebo/no treatment				
Mucositis (any) 0-4 scale Follow-up: median 28 days	**Low risk population**[1]		**RR 0.76** (0.47 to 1.24)	454 (4 studies)	⊕⊕◯◯ **low**[2,3]	
	600 per 1000	**456 per 1000** (282 to 744)				
	High risk population[1]					
	950 per 1000	**722 per 1000** (446 to 1000)				
Mucositis (severe) 0-4 scale Follow-up: median 28 days	**Low risk population**[4]		**RR 0.82** (0.54 to 1.23)	244 (4 studies)	⊕⊕◯◯ **low**[5,6]	
	300 per 1000	**246 per 1000** (162 to 369)				
	High risk population[4]					
	650 per 1000	**533 per 1000** (351 to 800)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Based on the range of absolute risk of developing any mucositis of patients (with different cancer types and treatments) in the control groups of the included studies.
[2] One study at low risk of bias and three unclear.
[3] Substantial heterogeneity Chi squared 30.49, df=3, P<0.0001, I squared = 90%.
[4] Based on the range of absolute risk of developing severe mucositis of patients (with different cancer types and treatments) in the control groups of the included studies.
[5] One high risk of bias, two unclear and one low
[6] Moderate heterogeneity Chi squared 7.44,df=3, P=0.06, I squared = 60%, with some inconsistency (only one study, at unclear risk of bias, showing benefit)

DISCUSSION

Summary of main results

This update has identified a further 42 included trials which have been published in less than 3 years, bringing the total number of included studies up to 131. The trials included in this review have evaluated 43 different interventions and recruited a total of 10,514 patients.

There is some evidence of a benefit for cryotherapy (ice chips) and keratinocyte growth factor based on a body of evidence comprising at least 6 trials and at least 550 participants for each of these interventions. However all these trials were assessed as being at either high or unclear risk of bias.

- **Cryotherapy** was found to be beneficial in the prevention of all the outcome categories of mucositis. Specifically the prevention of any mucositis RR = 0.74 (95% CI 0.57 to 0.95, P = 0.02), moderate plus severe mucositis RR = 0.53 (95% CI 0.31 to 0.91, P = 0.02), and severe mucositis RR = 0.36 (95% CI 0.17 to 0.77, P = 0.008).
- **Keratinocyte Growth Factor** was found to be beneficial for the prevention of all the outcome categories of mucositis, with RR = 0.82 (95% CI 0.71 to 0.94, P = 0.005) for any mucositis, RR = 0.74 (95% CI 0.62 to 0.89, P = 0.002) for moderate plus severe mucositis and RR = 0.72 (95% CI 0.58 to 0.90, P = 0.004) for severe mucositis.

There is weak unreliable evidence of a benefit for the following eight interventions based on a smaller body of evidence (2 to 5 trials) involving 90 to 350 participants. Most of the trials in this group are assessed as being at either high or unclear risk of bias.

- **Aloe vera:** weak unreliable evidence that solution was beneficial for the prevention of moderate to severe mucositis: RR = 0.74 (95% CI 0.58 to 0.96; P = 0.02).
- **Amifostine **:** weak unreliable evidence from 11 low quality trials (8 trials high risk of bias and 3 unclear risk of bias) that amifostine is beneficial for the prevention of any mucositis: RR = 0.95 (95% CI 0.91 to 0.99, P = 0.007) and moderate to severe mucositis: RR = 0.75 (95% CI 0.58 to 0.96, P = 0.02).
- **Glutamine (intravenous):** weak unreliable evidence that glutamine administered intravenously is beneficial for the prevention of severe mucositis (RR = 0.25, 95% CI 0.10 to 0.62).
- **Granulocyte - Colony Stimulating Factor *:** (G-CSF) weak evidence that G-CSF is effective for the prevention of severe mucositis (RR = 0.36, 95% CI 0.15 to 0.86, P = 0.02) based on two small trials at low risk of bias
- **Honey:** weak unreliable evidence, with substantial heterogeneity, that honey may be beneficial in the prevention of any mucositis (RR = 0.70, 85% CI 0.56 to 0.88, P = 0.002), moderate to severe mucositis (RR = 0.48, 95% CI 0.31 to 0.74, P = 0.0009) and severe mucositis (RR = 0.26, 95% CI 0.13 to 0.52, P = 0.0002).
- **Laser:** weak unreliable evidence that laser is beneficial for the prevention of severe mucositis: RR = 0.20 (95% CI 0.06 to 0.62, P = 0.006).
- **Polymixin/Tobramycin/Amphotericin (PTA) lozenges/ paste *:** weak unreliable evidence that PTA lozenges may be beneficial for the prevention of any mucositis: RR = 0.87 (95% CI 0.78 to 0.96, P = 0.008).
- **Sucralfate:** evidence that sucralfate is effective in the prevention of severe mucositis, with a 33% reduction in severe mucositis in the sucralfate group compared to placebo (RR = 0.67, 95% CI 0.48 to 0.92, P = 0.01)

* Conclusions based on at least one trial with a low risk of bias.
** Conclusions based on larger body of weak unreliable evidence.

The mechanisms by which these ten interventions act to either prevent mucositis or reduce the severity of mucositis in cancer patients receiving treatment, is not clearly established. There are various explanations put forward in the literature, as to how the 'effective' interventions listed above might mitigate the effects of cancer treatment on the oral mucosa, but it is beyond the scope of this systematic review to comment further.

Overall, three interventions (aloe vera, PTA antibiotics and honey) were investigated almost exclusively in patients with head and neck cancer undergoing radiotherapy. Cryotherapy was investigated solely in patients with haematological malignancies undergoing chemotherapy or stem cell transplantation. Sucralfate was investigated mostly in patients with head and neck cancer undergoing radiotherapy, with a minority of trials including participants with other cancer types.The remainder (amifostine, granulocyte-colony stimulating factor, intravenous glutamine, keratinocyte growth factor, and laser treatment) were tested in combinations of patients with head and neck cancer, other solid tumours and haematological malignancies undergoing radiotherapy, stem cell transplantation, non-myeloablative chemotherapy or a combination.

Of the chemotherapeutic agents used to treat cancer, 5-fluouracil was the most frequently reported. However, a wide variety of different agents and schedules were examined, precluding analysis specific to a particular chemotherapy regimen.

It is important to note that a substantial body of evidence concerning chlorhexidine, has clearly shown no evidence of a benefit compared to either placebo or no treatment.

- **Chlorhexidine** - no evidence of a benefit for chlorhexidine based on 9 trials including a total of more than 650 participants. Risk of bias was assessed as low in 3 trials, high in one trial, and unclear in the remaining five trials.

In conclusion, there is some evidence of the effectiveness of cryotherapy and keratinocyte growth factor, and weaker evidence of a benefit associated with aloe vera, amifostine, glutamine (intravenous), granulocyte-colony stimulating factor, honey, laser, PTA antibiotic pastille/paste and sucralfate. There is no evidence of a benefit associated with the use of chlorhexidine.

Overall completeness and applicability of evidence

The number and range of interventions studied and reported in this review indicate the importance of this condition to clinicians and patients and the lack of a well-defined and effective means of prevention of oral mucositis in cancer patients. The presumed modes of action of the different interventions are very varied and include free radical scavenging (amifostine), local vasoconstriction (cryotherapy), reductions in concurrent mucosal infection (antibiotic pastilles) and enhancement of wound healing (honey, keratinocyte growth factor). Nine of the 43 interventions examined were found to have some evidence of a benefit, albeit sometimes weak, in preventing or reducing the severity of mucositis.

Despite the large number of trials included in the review few interventions were studied by several independent groups. This has led to limitations in the strength and generalisability of the evidence and several groups have highlighted the need for a co-ordinated research agenda (Wright 2003). The eligible trials varied in their setting, design, country of conduct, financial support and quality. The majority (79%) were conducted primarily by medical teams who did not report the involvement of dental practitioners. It was unfortunate that many studies presented data in a format unsuitable for meta-analysis in this review. The use of structured abstracts and adherence to the Consolidated Standards of Reporting Trials (CONSORT) guidelines would greatly improve the conduct and reporting of randomised controlled trials (RCTs), allowing a greater number to be included in future meta-analyses (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. This review has focused heavily on the prevention of mucositis in adults due to a lack of true RCTs conducted in paediatric populations, highlighting the difficulties of conducting research in this patient population.

Quality of the evidence

All studies included in this update of the review were assessed for risk of bias in six categories: adequate sequence generation, adequate allocation concealment, blinding (of patients, carers and outcome assessors), incomplete outcome data addressed, free of selective reporting and free of other bias. Overall risk of bias was described for each included study. Studies were deemed to be at low risk of overall bias if they were assessed as being at low risk for both allocation concealment and outcome assessor blinding. Only 10 studies (7.6%) met both criteria. Eighty-three studies (63.4%) were described as being at unclear overall risk of bias. The remaining 38 studies (29%) were found to be at high overall risk of bias. In general, methods of allocation concealment were not reported in publications, or poorly described by authors, which prevented the study being described as at low risk of bias for this category. The use of adequate allocation concealment, together with the publication of full descriptions of any methods used, needs to be incorporated into future trials. Of the 77 studies described as double blind, only 19 studies specifically stated that the outcome assessor was blinded. Adequate outcome assessor blinding is crucial to obtain unbiased assessments, even with the most objective of assessment instruments. It is both possible and highly desirable that future trials employ adequate outcome assessor blinding, even where blinding of patients or support staff to the intervention is impossible.

Although there was general consistency among the included studies in the number of categories of mucositis severity, scoring systems were not always clearly defined. The most frequently used assessment instrument in this review was the World Health Organization (WHO) score, followed by the Radiation Therapy Oncology Group (RTOG) instrument. Since our last review update, a systematic review has been published (Gibson 2010) which identified 54 oral assessment instruments in the literature. In order for the results of future studies to be synthesised with others, it is recommended that authors should employ a 'simple' assessment, in addition to any multicomponent instrument, to allow for data to be dichotomised.

The appearances of mucositis and oral candidiasis can be similar, and moreover, the two frequently co-exist. Consequently, if the assessors were lacking experience in the differential diagnosis of these oral lesions, the validity of mucositis scores may have been compromised. Candidiasis was not routinely screened for or reported in the trials included in this review, and the addition of candidiasis screening may assist in the differential diagnosis and treatment of the two conditions.

The reporting of secondary outcomes other than mucositis severity was variable and these outcomes were mentioned more frequently in trials published within the last 5 years. The types of outcome reported have changed to reflect characteristics of greater clinical relevance to clinicians and patients (Bellm 2002; Chang 2003; Sonis 2004; Wright 2003). In addition to reporting mucositis-related outcomes some groups reported known side effects of the interventions. For some trials these side effects were reported only in the intervention group and it was not clear if there were any events in the control group. In future trials these side effects should be measured and reported on all patients in both groups in a consistent manner. This adverse event data should be presented per patient and not per episode.

Potential biases in the review process

The meta-analyses in this review include only studies where mucositis outcomes were graded on a 0-4 scale. The most recent update of the review has also included a further 13 studies where the outcomes are recorded in Additional Table 2, and the results

are incorporated into the text of the review. However, 16 trial reports were excluded from this systematic review because the authors collected outcome data using an instrument which individually graded components of oral health, to produce a composite score (Eilers 1988). As such instruments include in the total score categories such as teeth and voice, the scores are not comparable with scales that measure only mucositis.

A further 16 trials are awaiting classification pending further information being made available by the authors of the papers and it is hoped that these trials may be included in future updates of this review.

Agreements and disagreements with other studies or reviews

This updated systematic review has identified nine interventions for the prevention of mucositis for which there is evidence of effectiveness. Four of these interventions: amifostine, locally applied antibiotic (PTA), cryotherapy and keratinocyte growth factor, have also been identified as having some evidence of effectiveness by practice guidelines and other systematic reviews (Keefe 2007; McDonnell 2007; Sasse 2006; Stokman 2006). We have also found weak evidence to support the effectiveness of the use of aloe vera, granulocyte-colony stimulating factor and honey for the prevention of oral mucositis, but we are not aware of other systematic reviews which support the use of these interventions.

Regarding the use of laser for the prevention of mucositis there is evidence based on two studies that laser reduces the incidence of severe mucositis, a finding which is supported by a Cochrane review on the treatment of oral mucositis which found that laser treatment was effective in reducing the severity of established mucositis (Clarkson 2010).

Our systematic review includes a small study by Oberbaum 2001 (n = 32) which is also included in another systematic review by Kassab 2009 which evaluated homeopathic interventions for the adverse effects of cancer treatments. In their review, Kassab et al reported the mucositis outcome as mean area under the curve for each group, and found a statistically significant difference favouring traumeel, the homeopathic intervention. In our systematic review we used a different outcome category: prevention of any mucositis, and found no statistically significant difference between traumeel and placebo. Both reviews assessed this study as being at low risk of bias. We agree with Kassab et al that further research is required to confirm any benefit of this intervention.

Our updated systematic review has found some weak evidence for the effectiveness of intravenous glutamine in the prevention of severe oral mucositis, based on three trials that have been published since 2006, but this intervention is not recommended by the current Multinational Association of Supportive Care in Cancer (MASCC) guidelines, based on a single study from 2002 (Keefe 2007). There are plans to update these guidelines in the near future.

AUTHORS' CONCLUSIONS

Implications for practice

Cryotherapy (ice chips) and Keratinocyte Growth Factor (Palifermin®) have shown some evidence of benefit in the prevention of mucositis. There is weaker less reliable evidence of a benefit associated with aloe vera, amifostine, intravenous glutamine supplementation, granulocyte-colony stimulating factor, honey, laser, polymixin/tobramycin/amphotericin (PTA) lozenges and sucralfate.

There is no evidence that chlorhexidine is more effective that placebo and this intervention should not be used in the prevention of mucositis.

The patient groups studied were diverse, the associated treatment modalities were varied and the strength of the evidence of effectiveness was variable. As some interventions were studied exclusively in certain patient groups receiving specific treatment modalities generalisation of the results to other tumour types and treatment modalities must be done with caution as some benefits may be specific to certain cancer types and treatments.

Implications for research

There is a need for well designed and conducted trials of interventions to prevent mucositis induced by chemotherapy, radiotherapy or targeted therapies. Such trials should be reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent. This review has highlighted several interventions (aloe vera, amifostine, G-CSF, PTA antibiotic pastille/paste, cryotherapy, intravenous glutamine, honey, keratinocyte growth factor and laser therapy) with evidence of effectiveness from more than one trial included in a meta-analysis. Further research into the benefits and harms of these interventions and whether these results can be generalized to other forms of cancer and its treatment should be conducted. In addition, as several agents were reported to show efficacy in a single trial, further well designed, adequately powered randomised controlled trials of these and other novel agents for mucositis prevention should be undertaken. The concurrent use of two or more interventions, with different modes of action, may be worth evaluating in well conducted, adequately powered randomised controlled trials.

We recognise the importance of multicomponent indices for oral health. However, to facilitate comparison between interventions for preventing mucositis it would be helpful if researchers used a simple mucositis index with a 0-4 scale (e.g. World Health Organization (WHO), Radiation Therapy Oncology Group (RTOG), National Cancer Institute - Common Toxicity Criteria (NCI-CTC)) as part of their outcome evaluation.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abbasi-Nazari 2007

Methods	Randomised, parallel group multicentre study conducted in Iran. Unclear if dentist involved in the study. Drop outs: unclear. Duration: 42 days
Participants	Adults with cancers of the oral cavity, nasopharynx or hypopharynx treated with radiotherapy or chemoradiotherapy (Cisplatine). Data presented for 24 patients. No dates for start and finish of recruitment
Interventions	2 groups: placebo versus allopurinol mouthrinse. 10 mL of solution rinsed three times a day for three minutes. Solution then discarded
Outcomes	Authors state that mucositis was graded weekly using the WHO instrument. However, the instrument reproduced in the publication is not the WHO instrument. Other reported outcomes: None
Notes	Funding source: pharmaceutical.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A dynamic randomization procedure was utilized to divide patients to receive allopurinol mouthwash (treatment group) or placebo mouthwashes (control group)" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.

Abbasi-Nazari 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Patients who experienced hypersensitivity reaction or serious side effects were excluded from the study. Also patients who complained about pain or other signs attributed to severe mucositis were excluded from the study." Comment: 24 patients included in analysis. However, it is unclear how many patients were recruited
Selective reporting (reporting bias)	Unclear risk	Data presented for 24 patients for grade of mucositis by grade of mucositis by week for each arm of the study (figures 1 and 2) . However, it is unclear how many patients were initially recruited
Other bias	High risk	Significant gender imbalance between the arms of the study (P = 0.028) Authors state that they used to WHO instrument. However, this is not the instrument presented in table 1

Ahmed 1993

Methods	Randomised, parallel group study conducted in USA. Unclear whether dentist was involved in study
Participants	Adults with haematological malignancies prior to BMT after conditioning with etoposide. 12 enrolled and completed
Interventions	2 groups, placebo versus propantheline (30 mg every 6 hours during infusion and 12 hours after, for total of 6 doses)
Outcomes	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
Notes	All patients received conditioning regimen of etoposide, cyclophosphamide and carmustine, together with acyclovir, and nystatin or clotrimazole. Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned". Comment: random component not described.

Ahmed 1993 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Unclear risk	Quote: "Trial drugs were administered blind". Comment: unclear who was blind.
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Quote: "Assessment of mucositis severity was performed by two independent observers" Comment: unclear if they were blinded to allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12 patients randomised. Authors do not give information about drop outs. Unclear how many patients in each arm. Unclear how many patients included in results
Selective reporting (reporting bias)	Unclear risk	Brief mucositis data presented in text (enough for use in mucositis absent versus present dichotomy)
Other bias	Low risk	Study appears to be free of other sources of bias.

Anderson 1998

Methods	Randomised, cross-over study conducted in USA. Unclear if dentist was involved in study. Duration 14 days. Recruitment May 1993 to April 1996
Participants	Children and adults with solid cancer (sarcoma/blastoma) who have previously had chemotherapy and experienced mucositis. 24 patients eligible and enrolled, 13 completed
Interventions	2 groups, glycine control (described as placebo) versus glutamine (4 ml/M² twice daily swish and swallow) for 14 days
Outcomes	Mucositis (patient's description on 0-4 scale). Grade >= 2 painful mucositis which altered food intake. Assessment used: day 14. Other reported outcomes: none
Notes	Funding source: charity/university.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Anderson 1998 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were assigned randomly to two courses of glutamine and two courses of glycine" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Low risk	Quote: "In addition to the patients, the nurses and oncologists involved in the care of these patients also were blinded" Comment: probably done.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	High risk	24 patients randomised. Paired outcome data available for 13 patients. Authors give full reasons for attrition/exclusion. Potential for overall estimate to be reversed if excluded patients were included
Selective reporting (reporting bias)	Unclear risk	Data presented for total days of mucositis compared to patient age and days of mucositis > grade 2 by chemotherapy regime
Other bias	Low risk	Study appears to be free of other sources of bias.

Antonadou 2002

Methods	Randomised, parallel group study conducted in Greece. Clear information on withdrawals: 3/26 control, 2/24 intervention. Dentist not involved in study. Drop outs: 10%. Duration 3 months
Participants	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 between January 1997 and January 1998. 45 completed
Interventions	2 groups, no treatment control versus amifostine 300 mg/m2 15-30 min before radiotherapy for 6-7 weeks

Antonadou 2002 (*Continued*)

Outcomes	Mucositis assessed weekly EORTC criteria. Assessment used: day 28. Other reported outcomes: dysphagia, xerostomia, treatment interruptions, haematological changes, side effects (nausea, transient hypotention)
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were randomized (1:1) to receive radiochemotherapy plus amifostine (study group) or radiochemotherapy" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Comment: amifostine versus no intervention. No apparent blinding
Blinding (performance bias and detection bias) Patients	High risk	Comment: amifostine versus no intervention. No apparent blinding
Blinding (performance bias and detection bias) Outcome assessors	High risk	Comment: amifostine versus no intervention. No apparent blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	50 patients randomised. Assessable data from 45 patients. 2/24 in the amifostine group and 3/26 in the control group. Authors give full reasons for attrition and exclusion
Selective reporting (reporting bias)	Low risk	Data presented for 45 patients by mucositis grade (table 4).
Other bias	Low risk	Study appears to be free from other sources of bias.

Antunes 2007

Methods	Randomised, parallel group study conducted in Brazil. Study conducted between January 4th 2004 and May 20th 2005. Dentist involved in study
Participants	Adults with leukaemia, lymphoma or myelodysplastic syndrome undergoing HSCT. 38 patients recruited and completed
Interventions	2 groups, lazer (50 mW InGaAlP diode laser, emitting continuous light at 660 nm, with a real power output of 46.7 mW and energy density (ED) of 4 J/cm2, measured at the fiberoptic end with 0.196 cm2 of section area) versus sham laser control
Outcomes	Mucositis incidence (OMAS, WHO), correlation between OMAS and WHO, mucositis free survival, ulcerative area extension, evaluator agreement, pain, clinical outcomes
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised on the day of admission for the transplantation, between receiving laser therapy, or not receiving laser therapy" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Low risk	Quote: "the dentists were the only members of the team who knew which group the patient was randomized to" Comment: probably done.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "the dentists were the only members of the team who knew which group the patient was randomized to" Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "one dentist and 3 nurses (blinded for the study) performed daily oral evaluation of the patients" Comment: one outcome assessor was not blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	38 patients randomised. No missing outcome data.

Selective reporting (reporting bias)	Low risk	Data presented for all patients by mucositis grade (fig 1).
Other bias	Low risk	Study appears to be free from other sources of bias.

Arun Maiya 2006

Methods	Randomised, parallel group study conducted in India. Clear information about withdrawals: 0. Unclear if dentist involved in study. Duration: until the completion of radiotherapy. Recruitment took place between January 2003 and January 2004
Participants	Adults with carcinoma off the oral cavity receiving radiotherapy (66 Gy in 33 fractions)
Interventions	2 groups, analgesics, anaesthetics, 0.9% saline and chlorhexidine versus laser (632.8 nm, 10 mW) for 3 minutes, 5 days per week
Outcomes	Mucositis assessed weekly using the WHO score. Other reported outcome measures: pain
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the patients were divided based on computer generated randomization into laser (study group) and control group with 25 patients in each group." Comment: computer generated randomisation.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Neon laser versus oral analgesics, local application of anaesthetics, 0.9% saline and povidine wash. No apparent blinding
Blinding (performance bias and detection bias) Patients	High risk	Neon laser versus oral analgesics, local application of anaesthetics, 0.9% saline and povidine wash. No apparent blinding
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "Physician blinded to the type of treatment using WHO scale for mucositis and visual analogue scale for pain evalua-

Arun Maiya 2006 (*Continued*)

		tion recorded the objective assessment of the degree of mucositis weekly" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	50 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Data presented for all patients by arm and grade of mucositis in text (page 401)
Other bias	Unclear risk	No information given on characteristics of patients in each group at baseline. Amount of analgesics used in each group not reported

Attal 1993

Methods	Randomised, parallel group study conducted in France. Clear information on withdrawals: 6/70 control, 6/70 test. Unclear if dentist involved in study. Drop outs: 0%. Duration: day -8 to day +100
Participants	Adults with mixed blood cancers admitted to BMT unit. 140 patients enrolled 6 died in each group, but all were evaluated. Recruited December 1990 to September 1992
Interventions	2 groups, no treatment control versus pentoxifylline (oral PTX 1600 mg 1 per day in 4 doses)
Outcomes	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, septicaemia, 100 day survival
Notes	All patients received one of 4 possible standard regimens either; Cyclophosphamide +TBI, or cyclophosphamide + bisulfan, or melphalan + TBI or cyclophosphamide + etoposide + carmustine, prior to autologous or allogenic BMT. Funding source: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised to receive or not PTX. The treatment allocation for each patients was assigned by telephone by the biostatistics department, which had prepared before initiation of the trial a computer-generated sequence unknown to the physicians participating in the trial." Comment: computer generated randomi-

Attal 1993 (*Continued*)

		sation.
Allocation concealment (selection bias)	Low risk	Quote: "The treatment allocation for each patient was assigned by telephone by the biostatistics department." Comment: central method of allocation.
Blinding (performance bias and detection bias) Carers	High risk	PTX versus no treatment. No apparent blinding.
Blinding (performance bias and detection bias) Patients	High risk	PTX versus no treatment. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	The authors state that the physicians participating in the trial were unaware of the randomisation sequence. However, it is unclear who was doing the outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	140 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Data presented in the text for the number of patients with mucositis grade 2 or higher in each study arm
Other bias	Low risk	Study appears to be free of other sources of bias.

Bensadoun 1999

Methods	Randomised, parallel multisite study conducted in France. Clear information about withdrawals: 0. Dentist involved in study. 30 patients recruited between September 1994 and March 1998. Duration: 5 consecutive days each week during the 7 weeks of radiotherapy
Participants	Adults with head and neck cancers receiving radiotherapy (at least 65 Gy in total)
Interventions	2 groups, sham laser versus laser (wavelength: 632.8 nm; power: 60 mW in Nice and Mareilles, 25 mW in Reims)
Outcomes	Mucositis assessed weekly using the WHO scale. Other outcome measures: pain, ability to swallow, incidence and duration of treatment gaps
Notes	Funding source: unclear.
Risk of bias	

Bensadoun 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were assigned to either laser treatment or sham-treatment by computer blocked randomisation, 15 in each arm" Comment: computer generated randomisation.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Low risk	Quote: "this operator was the only person to know whether or not the patients was being sham treated, and did not participate in the evaluation and scoring of mucositis" Comment: unlikely that nursing staff would know of allocation
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "Objective assessment of degree of mucositis was recorded weekly by a physician blinded to the type of treatment the patient received" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	30 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for mean grade of mucositis by arm by week of treatment (table 3/ fig 3) and distribution of mucositis grades, in number of weeks, for both treatment weeks
Other bias	Unclear risk	Possible imbalance of groups at baseline laser group older (mean 62.7 vs 58.1). Also 12/15 of laser group vs. 6/15 of placebo group received laser treatment to skin of neck ("possible distant laser effect"). Different power of laser used at one study site (Relms)

Biswal 2003

Methods	Randomised, parallel group study conducted in Malaysia. Clear information on withdrawals. Unclear if dentist was involved in study. Drop outs: 0%. Duration: 49 days
Participants	Adults with head and neck cancer. 40 patients recruited and evaluated. Recruited November 2000 to October 2001
Interventions	2 groups, rinse then swallow 20 ml natural honey before radiotherapy, 20 ml after and 20 ml 6 hours after that versus no treatment control
Outcomes	Mucositis RTOG grading. Other reported outcomes: weight gain
Notes	Funding source: university. All patients received radiotherapy 60-70 Gy over 6-7 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "twenty patients were allocated equally to one study arm and another 20 to the control arm by computer generated random numbers" Comment: computer generated random numbers.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Honey versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Patients	High risk	Honey versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Honey versus no intervention. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Data presented for number of patients with mucositis, number of patients with grade 3/4 mucositis, mean grade, mean onset and mean total duration (all table 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Bjarnason 2009

Methods	Randomised parallel group multisite study conducted in Canada. Clear information about withdrawals. Dentist involved in study. Recruitment of patients took place between August 1999 and November 2004
Participants	Adults with head and neck cancers receiving radiotherapy (50-70 Gy)
Interventions	2 groups, radiotherapy in the morning (8am to 10am) versus radiotherapy in the evening (4pm to 6pm)
Outcomes	Mucositis assessed weekly using the OMAS instrument. Other reported outcomes: disease reoccurrence, quality of life, compliance with treatment, death, smoking status, weight loss
Notes	Funding source: National Cancer Institute of Canada.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A minimization procedure was used to randomize patients" Quote: "patients were stratified by treatment centre, pretreatment smoking behaviour...tobacco use questionnaire, and planned total radiation dose" Comment: minimization.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Morning versus evening radiation. No apparent blinding.
Blinding (performance bias and detection bias) Patients	High risk	Morning versus evening radiation. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "the oncologists performing the evaluations were aware of the treatment arm for each patient"
Incomplete outcome data (attrition bias) All outcomes	Low risk	216 patients recruited. 7 patients deemed ineligible (4/108 arm A, 3/108 arm B), 3 patients in arm A did not receive radiotherapy (3/108 arm A), 1 patient in arm B did not have mucositis assessment. 205 patients included in final analysis

Bjarnason 2009 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Data presented for number of patients with grade 3 or greater mucositis, median interval to mucositis and median grade of mucositis (all RTOG). Data collected using OMAS instrument also presented (table 3)
Other bias	Low risk	Study appears to be free from other sources of bias.

Blazar 2006

Methods	Randomised, parallel group, multisite study conducted in the USA. Clear information about withdrawals: 20 (17 patients withdrew and were replaced). Unclear if dentist involved in study
Participants	Adults and children with haematological malignancies (acute lymphoblastic leukaemia, acute myelogenous leukaemia, chronic myelogenous leukaemia, myelodysplastic syndrome, non-Hodgkin leukaemia, Hodgkin's disease, other) aged between 3 and 65 years old, receiving allogeneic hematopoietic stem cell transplantation. Conditioning regimes: cyclophosphamide and total body irradiation or busulfan and cyclophosphamide
Interventions	3 cohorts, cohort 1 received either palifermin (60 μg/kg in 6 doses), palifermin (40 μg/kg in 6 doses) or placebo. Cohort 2 received palifermin (60 μg/kg in 9 doses) or placebo. Cohort 3 received palifermin (60 μg/kg in 12 doses)
Outcomes	Mucositis assessed weekly using the world health organisation and common toxicities criteria scales. Other reported outcome measures: adverse events, GVHD, hematopoietic recovery, methotrexate dosing, survival and relapse
Notes	Funding source: National Institute of Health grants and Amgen (pharmaceutical)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was structured to achieve balance between the placebo and palifermin groups within each study site in each cohort" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Blazar 2006 (*Continued*)

Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	100 patients randomised. 17 patients discontinued and replaced (1/31 placebo group). 3 patients suffered SAE and were not replaced (1/31 placebo group). Full reasons given for attrition/exclusion
Selective reporting (reporting bias)	Low risk	Data presented for all patients by mucositis grade. Palifermin doses combined (table 4)
Other bias	Low risk	Study appears to be free of other sources of bias.

Borowski 1994

Methods	Randomised, parallel group study conducted in France. Clear information on withdrawals: 7/82 control, 9/84 test. Dentist involved in study. Duration: 30 days
Participants	Children and adults with mixed cancer and candidates for BMT. 166 eligible and enrolled between February 1986 and November 1989 with 150 completing
Interventions	2 groups, limited oral hygiene versus intense oral hygiene (brushing 3 times per day after meals as instructed by dentist)
Outcomes	Moderate or severe mucositis with detailed description of each category. Assessment used: day 30. Other outcomes: plaque, fever, septicaemia
Notes	Chlorhexidine mouthrinse used at least 5 times daily by both groups. Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients fulfilling the enrolment criteria were randomly allocated by telephone" Quote: "randomisation was balanced every 4 subjects and stratified on IOS." Comment: random component not described.

Borowski 1994 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "Patients fulfilling the enrolment criteria were randomly allocated by telephone" Comment: central allocation.
Blinding (performance bias and detection bias) Carers	High risk	Intensive oral hygiene versus limited oral hygiene. No apparent blinding
Blinding (performance bias and detection bias) Patients	High risk	Intensive oral hygiene versus limited oral hygiene. No apparent blinding
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "these evaluations could not be performed blindly because of dental plaque."
Incomplete outcome data (attrition bias) All outcomes	Low risk	166 patients randomised. 16 patients excluded from analysis: 9/ 84 intensive oral hygiene group, 7/82 limited oral hygiene group. Authors give complete reasons for exclusion/attrition
Selective reporting (reporting bias)	Unclear risk	Data presented in the text for proportions of patients with moderate/severe mucositis according to treatment allocation. Percentage of patients with moderate or severe mucositis presented over time for both arms of the study (fig 2) and patients receiving TBI/no TBI (fig 1)
Other bias	Low risk	Study appears to be free of other sources of bias.

Bourhis 2000

Methods	Randomised, parallel group study conducted in France. Unclear information on withdrawals: 1 died and 1 refused, unclear which group. Unclear if dentist involved in study. Drop outs: 8%. Duration: unclear
Participants	Adults with head and neck cancer, stage IV not amenable to conventional radiosurgical treatment. Karnofsky performance > 60. Radiotherapy 64 Gy in 22-23 days. 26 patients enrolled and randomised between May 1996 and February 1998. 24 were evaluated
Interventions	2 groups, no treatment control versus amifostine (subcutaneous infusion 150 mg/m^2 amifostine administered IV twice daily 15-30 minutes prior to each radiotherapy session)

Bourhis 2000 (*Continued*)

Outcomes	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
Notes	RTOG index also given with mean duration of at least grade 3 mucositis. Funding source: pharmaceutical.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to receive or not 150mg/m2 amifostine 15-30 min prior to each radiation session." Comment: random component not described.
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation procedure was done by telephone". Comment: central allocation. Probably done.
Blinding (performance bias and detection bias) Carers	High risk	Comment: amifostine versus no intervention. No apparent blinding
Blinding (performance bias and detection bias) Patients	High risk	Comment: amifostine versus no intervention. No apparent blinding
Blinding (performance bias and detection bias) Outcome assessors	High risk	Comment: amifostine versus no intervention. No apparent blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	26 patients randomised. 2 patients not included in mucositis assessment. Full reasons for drop outs
Selective reporting (reporting bias)	Unclear risk	Data presented WHO grades 2 to 4 and mean duration of > grade 3 mucositis (days) (table 1)
Other bias	High risk	Study stopped early due to problems with the tolerance of amifostine

Brizel 2000

Methods	Randomised, parallel group multisite study conducted in USA, Germany and France. Clear information about withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration: 1 year
Participants	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. 315 enrolled and randomised between October 1995 to October 1997. 12 patients never received any treatment or follow-up. The results are presented for the remaining 303
Interventions	2 groups, no treatment control versus amifostine 200 mg/m2 daily 15-20 minutes prior to radiation
Outcomes	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
Notes	Funding source: pharmaceutical.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "three hundred fifteen patients were enrolled and randomised from October 1995 to October 1997" Quote: "Patients were randomized using a dynamic allocation process." Comment: random component not described, however, authors make reference to two articles on randomisation. Probably done
Allocation concealment (selection bias)	Low risk	Quote: "treatment assignment was determined by a phone call from the enrolling institution to the protocol sponsor" Comment: central allocation. Probably done.
Blinding (performance bias and detection bias) Carers	High risk	Quote: "open label".
Blinding (performance bias and detection bias) Patients	High risk	Quote: "open label".
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "open label".

Brizel 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	315 patients randomised. 12 patients never received intervention. 22 patients discontinued but included in efficacy analysis. 2/150 patients in amifostine group missing from mucositis analysis. Observed event risk not sufficient to have clinically relevant impact
Selective reporting (reporting bias)	Low risk	Data presented for 301 patients by grade of mucositis.
Other bias	Low risk	Study appears to be free of other sources of bias.

Brizel 2008

Methods	Randomised, parallel group multisite study conducted in the USA, Canada and Australia. Withdrawals unclear (see ROB). Unclear if dentist involved in study
Participants	Adults with stage III/IV or IV squamous carcinoma of the oral cavity, oropharynx, hypopharynx and larynx undergoing concurrent chemoradiotherapy. Radiotherapy given in 2 Gy fractions to 70 Gy, hyperfractionated radiotherapy given in 1.25 Gy fractions twice daily. Chemotherapy: cisplatin 20 mg/m^2 for 4 days and fluorouracil 1000 mg/m^2/d for 4 days (weeks 1 and 5 of radiotherapy).
Interventions	2 groups: placebo versus palifermin 60 μg once weekly during radiotherapy for 9 consecutive weeks
Outcomes	Mucositis assessed weekly using CTCAE (version 2). Other reported outcomes: dysphagia, xerostomia, radiotherapy breaks, supplemental nutrition, safety
Notes	Funding source: pharmaceutical.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A multicentre, double blind, randomised, placebo controlled study was conducted at 22 centres" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Brizel 2008 (*Continued*)

Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Ninety-nine of 100 patients who were randomly assigned (67 palifermin, 32 placebo received at least 1 dose of study treatment and were evaluated" Comment: 101 patients stated as randomised in figure 1. Table 1 gives baseline data for 99 patients Comment: 21 patients discontinued. 17/67 in palifermin group, 4/32 in placebo group. Authors give incomplete reasons for attrition/exclusion
Selective reporting (reporting bias)	Unclear risk	Data only presented for mucositis scores > 2 and > 3 (fig 2)
Other bias	High risk	Authors used NCI CTC tool to assess patients for first 12 weeks and then the RTOG late onset tool at weeks 14/16/18/20. This prevented direct comparisons between the groups

Bubley 1989

Methods	Randomised, parallel group study conducted in USA. Clear information about withdrawals: 0. Unclear if dentist involved in study
Participants	Adults with head and neck cancer. Prior positive titre to Herpes Simplex. Results presented for 57 patients
Interventions	2 groups, placebo versus acyclovir 200 mg tablets 12 hourly.
Outcomes	Mucositis assessed by nurse. Assessment used: unclear. Other reported outcomes: herpes simplex virus
Notes	Data presented separately for patients receiving chemo and radiotherapy. Funding source: pharmaceutical.

Bubley 1989 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization occurred on the basis of computer-generated random codes supplied by the sponsor of the study" Comment: computer generated randomisation sequence.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	57 patients recruited. All patients included analysis.
Selective reporting (reporting bias)	Unclear risk	Data presented for absent versus present dichtomy.
Other bias	Low risk	Study appears to be free of other sources of bias.

Buentzel 2006

Methods	Randomised, parallel group, multicentre study conducted in USA/Europe. Clear information on withdrawals: none. Unclear if dentist involved in study. Drop outs: 22%. Duration: up to 90 days
Participants	Adults with head and neck cancer. 132 enrolled and randomised between October 1996 to October 1998. 102 completed but ITT analysis presented
Interventions	2 groups, placebo versus intravenous amifostine (300 mg/m2 before carboplatin 70 mg/m2 and radiotherapy on days 1 to 5 and 21 to 25, and intravenous amifostine 200 mg/m2 or placebo before radiotherapy on 6 to 20 and 26 to 30/35 days)

Outcomes	Mucositis graded with reference to RTOG criteria on a 0-4 scale. Assessment used up to 90 days. Other reported outcomes: xerostomia, 1 yr locoregional failure, progression-free survival, overall survival, treatment related adverse events: vomiting, nausea, asthenia, allergic reaction, anaemia, phlebitis, leukopenia, hypotension, allergic reaction
Notes	Funding source: industry. Pharmacological company provided drug and organised randomisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned in a ratio of 1:1". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine "yes" or "no".
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine "yes" or "no".
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	132 patients randomised. 20/67 missing from treatment group, 9/65 missing from placebo group. 1 patient from each group not treated. Authors give full reasons for exclusions and withdrawals. ITT analysis. Mucositis data presented for 129 patients
Selective reporting (reporting bias)	Low risk	Data presented for 129 patients by mucositis grade (table 2)
Other bias	Low risk	Study appears to be free from other sources of bias.

Buntzel 1998

Methods	Randomised, parallel group study conducted in Germany. Clear information on withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration: 6 weeks
Participants	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
Interventions	2 groups, radiotherapy with or without amifostine (15 min infusion 500 mg preceded by antiemetic regimen of 12 mg dexamethasone and 8 mg ondansetron)
Outcomes	WHO mucositis grades 3/4. Assessment used: day 42. Other reported outcomes: xerostomia, dysphagia, loss of taste, dermatitis, haematological side effects
Notes	More data presented but included extra 11 patients in amifostine group who were not entered into study. Funding source: pharmaceutical.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "eligible patients were randomised to receive RCT±amifostine" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Amifostine versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Patients	High risk	Amifostine versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Amifostine versus no intervention. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	28 patients initially randomised. After positive results suggested an additional 11 patients were recruited to the amifostine arm. No missing outcome data
Selective reporting (reporting bias)	Low risk	Data presented for all patients by mucositis grade (see table 2)

Other bias	High risk	Quote: "In view of these positive results, an additional 11 patients were subsequently accrued to the amifostine arm."

Cartee 1995

Methods	Randomised, parallel group study conducted in USA. Unclear information on withdrawals: 5 withdrew, unclear from which groups. Dentist involved in study. Drop outs: 10%. Duration: 21 days
Participants	Adults with breast cancer stage IV, with combination of chemotherapy including 5-FU, adriamycin & methotrexate. First cycle of chemotherapy. 50 patients were enrolled and 45 were evaluated
Interventions	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
Outcomes	Mucositis (CALGB GRADE >= 3). Assessment used: day 15. Other reported outcomes: WBC, plasma GM-CSF
Notes	Doses 0.01, 0.10, 1.00, 10.00 were combined and compared with dose 0 (control). Funding source: government.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised by the Duke Centre Protocol office according to a block randomisation scheme and assigned a unique identifier number which designated the GM-CSF dose level to be received" Comment: random component not explicit. However, setting makes adequate randomisation likely
Allocation concealment (selection bias)	Low risk	Quote: "The patient supply of mouthwash was labelled to correspond with the assigned identifier number and dispensed by pharmacy. The patient assignment information was maintained by the pharmacy to perverse the study double blind" Comment: pharmacy controlled randomisation.

Cartee 1995 (*Continued*)

Blinding (performance bias and detection bias) Carers	Low risk	Adequate allocation concealment. Unlikely that carers would know of allocation
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	50 patients randomised. 5 patients withdrew. Authors give full reasons for withdrawals and exclusions, but do not state which arm patients were randomised to
Selective reporting (reporting bias)	Unclear risk	Data presented for grade 3 mucositis by dose (table 1).
Other bias	Low risk	Study appears to be free of other sources of bias.

Carter 1999

Methods	Randomised, parallel group study conducted in USA. Clear information on withdrawals: none. Dentist Involvement unclear. Drop outs: 0%. Duration: up to 4 months post radiotherapy
Participants	Adults with head and neck cancer receiving curative intent radiotherapy, Karnofsky performance > 60. 102 patients enrolled and 102 completed
Interventions	2 groups, placebo versus sucralfate (added as suspension of 1 gm sucralfate/15 ml solution) swish 2 minutes and swallow 4 times per day
Outcomes	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
Notes	Funding source: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to receive either sucralfate or placebo" Comment: random component not de-

Carter 1999 (*Continued*)

		scribed.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Quote: "Both radiation oncology staff and patients were blinded to assigned treatment" Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Quote: "Both radiation oncology staff and patients were blinded to assigned treatment" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	102 patients randomised. 16 patients withdrew. 7/50 placebo, 9/52 sucralfate. Authors give reasons for attrition/exclusion
Selective reporting (reporting bias)	Unclear risk	Data presented for grade 3 mucositis (table 3), time to healing of mucositis (figure 3) and cumulative fraction of patients with > grade 3 mucositis during treatment
Other bias	Low risk	Study appears to be free of other sources of bias.

Cascinu 1994

Methods	Randomised, parallel group study conducted in Italy. Clear information on withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration: unclear
Participants	Adults with solid cancer (GI & prostate). Chemotherapy: 5-FU. First course of chemotherapy. 84 patients eligible, enrolled and completed
Interventions	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
Outcomes	Mucositis (global assessment of physician's and patient's description on 0-4 scale). Assessment used: unclear

Cascinu 1994 (*Continued*)

Notes	Statistical handling of data incorrect as all cycles included but used data from first cycle. Funding source: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised to a control arm or to receive chemotherapy" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Ice chips versus no intervention. Blinding impossible.
Blinding (performance bias and detection bias) Patients	High risk	Ice chips versus no intervention. Blinding impossible.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Ice chips versus no intervention. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	84 patients randomised. No patients discontinued over first cycle (data used in meta-analysis)
Selective reporting (reporting bias)	Low risk	Data presented for all patients by mucositis grade for first cycle (see table 3)
Other bias	Low risk	Study appears to be free from other sources of bias.

Castagna 2001

Methods	Randomised, parallel group multicentre study conducted in France, Italy and Switzerland. Clear information about withdrawals: 2/53 sucralfate, 1/52 placebo. Unclear if dentist involved in study. Drop outs: 2.8%
Participants	Adults with mixed cancer (hospitalised for allogenic or autologous BMT). 105 enrolled, 102 completed
Interventions	2 groups, placebo (n = 51) versus 2 g sucralfate (n = 51) every 3 hours daily, swish and swallow, for a maximum of 7 mouthwashes

Castagna 2001 (*Continued*)

Outcomes	Mucositis grade 3-4. Other reported outcomes: duration, diarrhoea, caloric intake by oral nutrition	
Notes	Funding source: pharmaceutical.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients fulfilling the enrolment criteria ... were randomly allocated to the sucralfate or the placebo group. Randomisation was stratified on TBI" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	105 patients randomised. 3 patients withdrawn due to disease recurrence (2/53 Sucralfate, 1/52 placebo)
Selective reporting (reporting bias)	Unclear risk	Data presented in percentages for grades 3 and 4 mucositis, but stated that 51 patients in each group were evaluated (text)
Other bias	Low risk	Study appears to be free of other sources of bias.

Cengiz 1999

Methods	Randomised, parallel group study conducted in Turkey. Clear information on withdrawals: none. Dentist involved in study. Drop outs: 0%. Duration from beginning to end of radiotherapy
Participants	Adults with head and neck cancer. 28 patients enrolled and completed
Interventions	2 groups, placebo versus sucralfate (6 g sucralfate suspension mouthwash 4 doses orally before meals and bedtime)
Outcomes	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
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomised". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for 28 patients (18 sucralfate, 10 placebo). All randomised patients included in analysis
Selective reporting (reporting bias)	Low risk	Data presented for 28 patients by treatment allocation and grades of mucositis
Other bias	Low risk	Study appears to be free from other sources of bias.

Cerchietti 2006

Methods	Randomised, parallel group study conducted in Argentina. Clear information on withdrawals: none. Dentist involvement unclear. Drop outs: 0%. Duration: 60 days
Participants	Adults with head and neck cancer. Chemoradiotherapy - radiotherapy 2 Gy /day up to total 70 Gy, plus cisplatin and 5-FU daily on days 1-5 repeated every 3 weeks. 32 enrolled 29 randomised and completed
Interventions	2 groups, placebo versus glutamine. (patients intravenous L-alanyl-L-glutamine 0.4 g/kg weight/day on each day of chemo through a separate IV line)
Outcomes	Mucositis assessed by mean of 3 highest scores by Objective Mucositis Score (OMS) and the WHO grading system on a 0-4 scale. Mucositis graded once/week during chemo and every other day during CRT. Assessment used up to 60 days. Other reported outcomes: pain, feeding tubes, mucositis related hospitalisation, adverse drug effects, body weight change, incidence of local infections, tumour response
Notes	Funding source: industry and foundation. Pharmacological company provided drug and organised randomisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned (in a 1:1 ratio in blocks of 6) to receive, in a double blind methodology, either intravenous L-alanyl-L-glutamine or placebo" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	29 patients randomised. No missing outcome data.

Cerchietti 2006 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Data presented for intensity of objective mucositis developed (mean 3 highest OMS), patients with severe objective mucositis, and patients with mucositis WHO grade 4 (table 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Chi 1995

Methods	Randomised cross-over multisite study conducted in Taiwan. Clear information on withdrawals: 0. Unclear if dentist involved in study. Duration: 10 days (day 5 to day 14)
Participants	Adults with head and neck cancer undergoing chemotherapy (two cycles of cisplatin 20 mg/m^2/day, fluorouracil 800 mg/m^2/day and leucovorin 90 mg/m^2/day).
Interventions	2 groups, no therapy versus GM-CSF (4 μg/kg/day subcutaneously) crossed over for 2nd cycle
Outcomes	Mucositis assessed daily for 17 days (0-4 scale). Other outcome measures: tumour response rate, neutrophil and leukocyte counts, adverse events
Notes	Funding information: government.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficent information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficent information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	High risk	GM-CSF versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	High risk	GM-CSF versus no intervention. No apparent blinding.

Chi 1995 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	20 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data provided in text for percentage reduction in incidence of severe mucositis, the mean duration of severe mucositis
Other bias	Low risk	Study appears to be free from other sources of bias.

Choi 2007

Methods	Randomised, parallel group study conducted in Korea. Clear information about withdrawals: 0. Unclear if dentist involved in study. Drop outs: 0%. Recruitment September 2003 to August 2005
Participants	Adults with solid tumours receiving 5FU chemotherapy. 51 enrolled and randomised, all completed
Interventions	2 groups, glutamine 30 g/day as supplement administered enterally for 15 days, versus best supportive care. Patients in both groups received cryotherapy
Outcomes	Mucositis severity evaluated using 0-4 scale, CTCAE criteria, any mucositis, ≥ grade 2 mucositis, ≥ grade 3 mucositis, cost and adverse events
Notes	Funding source: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised by the clinical trials office, using stage of therapy as the stratifying variable" Comment: computer generated randomisation.
Allocation concealment (selection bias)	Unclear risk	Quote: "Packages containing anonymous treatment supplies for each patient were provided by the clinical trials office" Comment: unclear if packages were sequentially numbered.
Blinding (performance bias and detection bias) Carers	High risk	Quote: "open label trial".

Choi 2007 (*Continued*)

Blinding (performance bias and detection bias) Patients	High risk	Quote: "open label trial".
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "open label trial".
Incomplete outcome data (attrition bias) All outcomes	Low risk	51 patients recruited. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Data presented for 51 patients by grade of mucositis and treatment arm
Other bias	Low risk	Study appears to be free of other sources of bias.

Chor 2010

Methods	Randomised parallel group study conducted in Brazil. Clear information about withdrawals: 0. Dentist involved in study. Duration: 7 days (day -7 to day 0)
Participants	34 adults undergoing autologous transplantation. No disease or treatment information
Interventions	2 groups, sham laser (led) versus laser (diode laser of 50 mW AsGaA1 applied emitting continuous light at 660 nm)
Outcomes	Mucositis assessed daily from day-2 until discharge using the Tardieu scale. Other outcome measures: febrile episodes, cumulative probability of developing mucositis, length of hospital stay
Notes	Funding Source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Chor 2010 (*Continued*)

Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	34 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented in the text for the number of patients experiencing mucositis in each arm
Other bias	Low risk	Study appears to be free of bias.

Crawford 1999

Methods	Randomised, parallel group multicentre study conducted in USA. Unclear information on withdrawals (previously described): 6/110 placebo, 6/101 test. Dentist involvement unclear. Drop outs: 9%. Duration: from day 4 to day 17 of cycle
Participants	Adults with small cell lung cancer. 211 patients enrolled, 199 evaluated, 195 evaluated on first cycle
Interventions	2 groups: placebo (not described) versus filgrastim (230 ug/m^2)
Outcomes	WHO mucositis grades 0-4. Assessment used: day 21. Other reported outcomes: neutropenia, infections complications
Notes	Used first cycle data. Funding source: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised within each study centre to receive chemotherapy with either filgrastim or the equivalent volume of placebo" comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Crawford 1999 (*Continued*)

Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "patients remained on blinded study drug until the primary endpoint of the study, FN, was reached."
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "A blinded chart review confirmed the exclusion of dental and oral problems related to mucositis" Comment: outcome assessors presumed to be blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	211 patients randomised. 12 patients excluded (6/110 placebo, 6/101 intervention). 199 patients received at least one cycle of chemotherapy and were included in the efficacy analysis. Authors provide reasons for exclusions in linked paper
Selective reporting (reporting bias)	Unclear risk	Data presented for incidence of mucositis in percentages (present versus absent) for both treatment arms and time to first episode of mucositis.
Other bias	Low risk	Study appears to be free of other sources of bias.

Cruz 2007

Methods	Randomised parallel group study conducted in Brazil. Unclear information about withdrawals. Dentist involved in study. Duration: 5 consecutive days from initiation of chemotherapy. Recruitment ran from May 2003 to February 2005
Participants	Children aged between 3 and 18 years old. 62 patients recruited. 56 patients evaluated on second visit, 59 patients evaluated at the 3rd evaluation. 35 patients had leukaemia or lymphoma, 25 patients had solid tumours. All patients received chemotherapy, 24 patients also received a stem cell transplant
Interventions	2 groups, no treatment control versus laser (continuous 780 nm wavelength, 60 mW power, fluence 4 J/cm^2.
Outcomes	Oral assessments performed 3 times (days 1, 8 and 15) using the Common Toxicity Criteria National Cancer Institute toxicity scale (0-4 scale). Other reported outcomes: use of drugs to treat infection, food intake (kcal), nutritional status (BMI), buccal health (number of decayed, missing and filled teeth), white cell count, number of teeth brushing sessions

Notes	Funding information: government.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized to receive or not laser treatment according to group allocation" Comment: author contacted and replied that sequence was computer generated
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Laser versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Patients	High risk	Laser versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "oral mucositis was scored by the same investigator...who was blind to the randomisation allocation using the CTC NCI." Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	62 patients randomised. 2 patients excluded. Authors do not provide allocation information. 56 patients evaluated at 2^{nd} assessment. 59 patients evaluated at assessment 3. Authors give no reasons for omissions
Selective reporting (reporting bias)	Unclear risk	Data presented for 59 patients in text and fig 1.
Other bias	Low risk	Study appears to be free of other sources of bias.

Dai 2009

Methods	Randomised, parallel group study conducted in China. Clear information about withdrawals: 0. Unclear if dentist involved in study. Drop outs: 0%
Participants	Adults with head and neck cancer receiving radiotherapy. 42 enrolled and randomised between January 2008 to December 2008, all completed
Interventions	2 groups, YHD Humo Decoction (honeysuckle flower 15 g, forsythia fruit 9 g, scullcap root 15 g, glehnia root 15 g, lilyturf root 15 g, crude rehmannia root 15 g, figwort root 15 g, red peony root 10 g, red sage 10 g, milkvetch root 10 g, asiabell root 10 g, balloon flower root 10 g, arctium fruit 10 g, and liquorice 6 g). It was decocted in water, boiling down to 150 mL of decoction, one dose daily, administered in six times by keeping it in the mouth for 2 min and then swallowed. No treatment control. All patients gargled with 2% lidocaine before meals and at night
Outcomes	Mucositis severity evaluated daily using RTOG 0-4 scale and the highest grade reported. Unclear how often this was measured but results reported by grade of mucositis and as days to reach each RTOG grade
Notes	Funding source: government.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "They were randomised equally into the test group and control group" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Yangyin Humo Decoction (YHD) versus no treatment. No apparent blinding
Blinding (performance bias and detection bias) Patients	High risk	Yangyin Humo Decoction (YHD) versus no treatment. No apparent blinding
Blinding (performance bias and detection bias) Outcome assessors	High risk	Yangyin Humo Decoction (YHD) versus no treatment. No apparent blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	42 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Data presented for 42 patients by arm and grade of mucositis

Dai 2009 (*Continued*)

Other bias	High risk	Patients in the intervention group received a higher dose of radiation than those in the control group (P < 0.05) All Chinese medicine RCTs are now a cause for concern in light of the findings of Taixiang et al, 2007

Dazzi 2003

Methods	Randomised, parallel group study conducted in Italy. Clear information about withdrawals: 0. Unclear if dentist involved in study. Drop outs: 0%
Participants	Adults with solid cancer. 90 enrolled and randomised between July 1997 and February 2002, 90 completed
Interventions	2 groups, placebo versus GM-CSF mouthwash (150 ug/day) in 100 cl 4 times per day. Rinse 1 minute. All patients 0.2% chlorhexidine and amphotericin B
Outcomes	Mucositis severity evaluated daily using NCI CTC. Other reported outcomes: oral pain evaluated daily using visual scale and pain requiring opioids
Notes	Funding source: none (c).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomly allocated to the GM-CSF or the placebo group" Comment: random component not described.
Allocation concealment (selection bias)	Low risk	Quote: "Study suspensions were prepared by the pharmacy unit and provided to the bone marrow transplant patients." Comment: pharmacy controlled randomisation.
Blinding (performance bias and detection bias) Carers	Low risk	Comment: intervention and control were dispatched from pharmacy, unlikely that carers would have knowledge of allocation
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.

Dazzi 2003 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	90 patients randomised. ITT analysis used. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for incidence of stomatitis, incidence and duration of severe stomatitis, and patients judged maximum mucositis score (table 3)
Other bias	Low risk	Study appears to be free of other sources of bias.

Dickson 2000

Methods	Randomised, parallel group study conducted in USA. 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. Recruitment June 1995 to August 1997
Participants	Adults receiving bone marrow transplant (BMT) or peripheral blood progenitor cell transplant (PBPCT). 58 enrolled and evaluated with leukaemia or lymphoma
Interventions	2 groups, powdered sugar added to food or drink (placebo) versus glutamine (10 g doses mixed with food or liquid chosen by patient) 3 times daily (30 g/day)
Outcomes	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
Notes	Funding source: pharmaceutical supply product/small grants programme of Stanford University Hospital's Nursing Management Department

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "the BMT or PBPCT patients were registered with the data managers and randomly assigned to receive glutamine" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Dickson 2000 (*Continued*)

Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	58 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for median mucositis duration (days), median mucositis grade and mucositis grades 2-4 (in percentages)
Other bias	Low risk	Study appears to be free of other sources of bias.

Dodd 1996

Methods	Randomised, parallel group, multicentre study conducted in USA. Dentist involved in study. Duration: up to 3 months
Participants	Adults with solid cancer receiving chemotherapy. Followed for 3 cycles of chemotherapy. 303 eligible, 227 enrolled and evaluated
Interventions	2 groups: water control (described as placebo) versus chlorhexidine mouthrinse (0.12%, 20 ml, twice per day)
Outcomes	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: survival, cost, time to onset of mucositis, severity of mucositis
Notes	Severity of mucositis at onset measured. ITT analysis. Funding source: government and pharmaceutical.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Researchers used a randomised, double-blind, placebo controlled trial design" Comment: random component not de-

Dodd 1996 (*Continued*)

		scribed.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Low risk	Quote:"physicians and intervention nurses performed blinded assessments" Comment: probably done.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote:"physicians and intervention nurses performed blinded assessments." Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	227 patients randomised. 5 patients were ineligible. Final sample of 222 patients. 89 patients (40%) did not finish 3 cycles of chemotherapy. ITT analysis conducted
Selective reporting (reporting bias)	Unclear risk	Data presented for 222 patients for mucositis incidence, time to onset of mucositis and severity of mucositis (table 3)
Other bias	Low risk	Study appears to be free of other sources of bias.

Dorr 2007

Methods	Randomised, parallel group multisite study conducted in Germany. Clear information about withdrawals: 8 (4/36 wobe mugos; 4/33 placebo). Unclear if dentist involved in study. Duration: treatment continued until 5 days after radiotherapy. Recruitment conducted between June 1996 and May 2000
Participants	Adults with head and neck cancers undergoing radiotherapy (all patients received dose > 40 Gy)
Interventions	2 groups, placebo versus wobe mugos (papain 100 mg, trypsin 40 mg and chymotrypsin 40 mg), 3 x 4 tablets per day
Outcomes	Mucositis assessed weekly using the RTOG/ EORTC classification. Other reported outcomes: side effects, pain on swallowing, dysphagia, skin erythema, skin desquamation
Notes	Funding source: unclear. Figure 1 data used.
Risk of bias	

Dorr 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was performed with the software 'Rancode plus' in randomly permuted blocks at a ratio of 1:1" Comment: computer generated random numbers.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Quote: "triple blind". Comment: unclear who the third blind party was. Nurse or statistician?
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "triple blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "triple blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	69 patients randomised. 8 patients withdrew/excluded (4/36 wobe mugos; 4/33 placebo)
Selective reporting (reporting bias)	Unclear risk	Data presented for frequency distribution of oral mucositis by grade (fig 1, percentages, not clear if all participants included) , mean values of maximum scores (fig 2), and average mucositis score (fig 3)
Other bias	Low risk	Study appears to be free of other sources of bias.

Dozono 1989

Methods	Randomised, cross-over study conducted in Japan. Clear information on withdrawals: none. Unclear if dentist was involved. Drop outs: 0%. Duration: unclear
Participants	Adults with solid cancer receiving chemotherapy. 15 patients enrolled and completed both periods
Interventions	2 groups: no treatment control versus allopurinol mouthwash (carboxymethylcellulose (CMC-Na) 5 g and allopurinol 500 mg, water to 500 ml solution)
Outcomes	Japan Society for Cancer Therapy criteria for stomatitis 0-4 scale

Dozono 1989 (*Continued*)

Notes	Funding source: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the subject was randomised into allopurinol administration and control one by the envelope method" Comment: unclear if envelopes were sequentially numbered or suffled. Random component not described
Allocation concealment (selection bias)	Unclear risk	Envelope method of randomisation. Unclear if envelopes were opaque and sequentially numbered
Blinding (performance bias and detection bias) Carers	High risk	Allopurinol mouthwash versus no intervention. No apparent blinding
Blinding (performance bias and detection bias) Patients	High risk	Allopurinol mouthwash versus no intervention. No apparent blinding
Blinding (performance bias and detection bias) Outcome assessors	High risk	Allopurinol mouthwash versus no intervention. No apparent blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	15 patients randomised into cross-over study. No missing outcome data
Selective reporting (reporting bias)	Low risk	Data presented for grade of stomatitis for control and treatment arms by treatment regimen
Other bias	High risk	Risk of bias assessed from translation.

Duenas 1996

Methods	Randomised, parallel group study conducted in Mexico. Clear information on withdrawals: none. Unclear if dentist was involved in study. Drop outs: 0%. Duration: -4 to day 16
Participants	Adults with mixed cancer undergoing peripheral stem cell transplant, receiving high dose (ifosfamide, carboplatin, etoposide). 15 patients enrolled (16 course of chemotherapy) and completed

Duenas 1996 (*Continued*)

Interventions	2 groups, placebo versus misoprostol (racemic prostaglandin E1 analogue) 250 μg 3 times per day
Outcomes	WHO mucositis grades 0-4, candidiasis, days in hospital with range. Assessment used: day 16. Other reported outcomes: diarrohea, fever, days in hospital, duration of antibiotics
Notes	All patients received fluconazole prophylaxis. Also received ranitidine, ketoconazole & 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.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly assigned to receive misoprostol 250 mg three times a day by mouth, or identical tablets of placebo in the same schedule" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	15 patients randomised to receive 16 courses of chemotherapy. No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Data presented for severity of mucositis in a graph (figure 1)
Other bias	High risk	15 patients received 16 courses of radiotherapy. Data presented for 16 patients Study ended prematurely: interim analysis demonstrated a significant difference

		favouring placebo in the incidence and severity of mucositis

El Sayed 2002

Methods	Randomised, parallel group, multicentre study conducted in Canada. Clear information on withdrawals. Dentist not involved in study. Drop outs: 0%. Duration: over radiotherapy
Participants	Adults with head and neck cancer treated with radiotherapy to the oral cavity, pharynx or larynx. 137 enrolled randomised and completed
Interventions	2 groups, placebo versus antimicrobial lozenge (bacitracin, clotrimazole and gentamicin (BCoG) 1 lozenge qid, day 1 to end of radiotherapy)
Outcomes	Mucositis graded according to the OMAS scale extent of severe mucositis score, worst-ever grade of ulceration/pseudomembrane. Assessment used: time to development of severe mucositis. Other reported outcomes: number of treatment days lost, changes in body weight, worst-ever grade of oral toxicity measured in patient diary, general non-mucosal toxicity assessed by the investigator. Mucositis measured twice weekly using the NCI CTC v2 scoring scale and the OMAS scale. Assessment used up to 28 days. Other reported outcomes: oral pain and ability to swallow using 10 cm VAS, salivary flow rate, adverse events nausea and vomiting
Notes	Funding source: National Cancer Institute.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "enrolled patients were randomized". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias)	Low risk	Quote: "double blind". Comment: probably done.

El Sayed 2002 (*Continued*)

Outcome assessors		
Incomplete outcome data (attrition bias) All outcomes	Low risk	138 patients randomised. 1 patient (1/68 placebo) deemed ineligible. 4 patients removed from primary analysis due to missing data (1/69 BCoG, 3/68 placebo). 137 patients included in extent of severe mucositis analysis
Selective reporting (reporting bias)	Low risk	Data presented for severity of mucositis by grade of mucositis for all randomised patients (table 4)
Other bias	High risk	Variation in radiation protocols and standard care between sites

Elad 2006

Methods	Randomised, parallel group study conducted in Israel, from August 2002 to March 2003. Unclear information on withdrawals. Dentist involvement unclear. Drop outs: 13%. Duration: 28 days
Participants	Adults with mixed cancer. BMT, total body irradiation, chemotherapy, chemoradiotherapy. 45 enrolled and randomised 39 completed
Interventions	2 groups, placebo versus topical histamine gel (a semi viscous solution containing 0.12% w/w HDC (histamine dihydrochloride) in a carbomer-based vehicle). Patients instructed to use 5 ml (1 teaspoon) 4 times a day
Outcomes	Mucositis measured twice weekly using the NCI CTC v2 scoring scale and the OMAS scale. Assessment used up to 28 days. Other reported outcomes: oral pain and ability to swallow using 10 cm VAS, salivary flow rate, adverse events nausea and vomiting
Notes	Funding source: early part of study funded by industry, rest of funding unclear. All received standard oral care: chlorhexidine mouthrinse 2/day amphotericin B lozenges 4/day. Pharmacological company provided drug and organised randomisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were allocated at random to one of two treatment arms in a blocked randomisation schedule." Comment: random component not described.

Elad 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Low risk	Quote: "Patient, investigator and staff were blinded to the treatment assignment." Comment: probably done.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "Patient, investigator and staff were blinded to the treatment assignment." Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "Patient, investigator and staff were blinded to the treatment assignment." Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	45 patients randomised. 39 patients matched inclusion criteria for efficacy analysis. No information given about 6 withdrawals
Selective reporting (reporting bias)	Unclear risk	Data presented for maximum intensity, average intensity, and duration of mucositis. Incidence of mucositis > grade 2 (table 3)
Other bias	Low risk	Study appears to be free of other sources of bias.

Epstein 1989

Methods	Randomised, parallel group single site study conducted in Canada. Clear information on withdrawals: 6/24 placebo. Dentist involved in study. Drop outs: 12%. No information given about dates of recruitment. Duration: unclear
Participants	Adults with head and neck cancer receiving radiotherapy (25 patients received 4500 cGy in 15 daily fractions over 3 weeks, 18 patients received 6000 cGy in 25 daily fractions over 5 weeks). 49 patients enrolled, 43 patients completed
Interventions	2 groups, placebo (10% alcohol) base versus benzydamine (1.5 mg/ml benzydamine hydrochloride in a 10% alcohol base). Both groups asked to rinse 15 ml for 30 seconds, 4 times daily, and then expectorate
Outcomes	Multivariable scale (area of involvement, severity of inflammation, severity of ulceration and maximum size of ulceration each graded using a 0-3 scale. Scores then combined) . Other outcomes measures: pain (at rest and on eating), burning, anesthetic effect of benzydamine, salivary flow rate
Notes	Funding source: pharmaceutical.

Epstein 1989 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "the patients were selected randomly to receive drug (Bzd) or placebo rinse (carrier base only)" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "Drugs were dispensed in a double blind manner". Comment: insufficient information to determine 'yes' or 'no'
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	49 patients recruited. 43 included in analysis. 6 patients (all placebo) withdrawn due to non-compliance
Selective reporting (reporting bias)	Unclear risk	Data presented for maximum size of ulcerations, total area of ulcerations, average ulceration size and area of reaction x severity of inflammation/surfaces involved
Other bias	Low risk	Study appears to be free of other sources of bias.

Epstein 1994

Methods	Randomised parallel group study conducted in Canada. Clear information about withdrawals: 0. Dentist involved in study. Duration: 5-7 weeks
Participants	Adults with head and neck cancer receiving radiotherapy (either 5000 cGy in 16 fractions or 6000 cGy in 25 fractions). 33 patients randomised and completed study

Epstein 1994 (*Continued*)

Interventions	2 groups, placebo versus sucralfate (1 g/5 ml). Drug or placebo rinsed and swallowed for 1 or 2 minutes, 4 times daily	
Outcomes	Mucositis assessed weekly using a cumulative mucositis score (Epstein). Other reported outcome measures: compliance, pain, adverse events, dysphagia, xerostomia	
Notes	Funding source: pharmaceutical.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "following consent and randomisation". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	33 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for total mucositis score and total ulceration by arm
Other bias	Low risk	Study appears to be free from other sources of bias.

Epstein 2001

Methods	Randomised parallel group multisite study conducted in the USA and Canada. Clear information about withdrawals. Unclear if dentist involved in study. Duration: until 2 weeks after completion of radiotherapy
Participants	Adults with head and neck cancers receiving radiotherapy (total planned dose of 5000 Gy) or concomitant radiotherapy and chemotherapy (cisplatin, or 5-fluorouracil)
Interventions	2 groups, placebo versus benzydamine (0.15%, 1.5 mg/ml). Patients asked to rinse with 15 ml of mouthwash for 2 minutes, 4-8 times daily 173 patients randomised
Outcomes	Mucositis assessed at every clinic visit using a multivariable scale (Epstein). Other reported outcome measures: use of analgesics, mouth and throat pain, compliance, number of patients diluting rinses, adverse events, risk of mucositis, weight loss, number of patients needing nasogastric or percutaneous endoscopic gastrostomy tube feeds
Notes	Funding source: pharmaceutical.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Unclear risk	Placebo controlled study, however no blinding information is given
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Placebo controlled study, however no blinding information is given
Incomplete outcome data (attrition bias) All outcomes	Low risk	173 patients randomised. 172 patients treated. 165 patients (who had received at least 1 on-radiation evaluation) included in ITT analysis
Selective reporting (reporting bias)	Unclear risk	Data presented for mean AUCs by radiotherapy interval.

Epstein 2001 (*Continued*)

Other bias	Low risk	Study appears to be free from other sources of bias.

Ertekin 2004

Methods	Randomised, parallel group study conducted in Turkey, between May 2001 and May 2002. Clear information about withdrawals, 3 in placebo. Dentist not involved in study. Drop outs: 10%
Participants	Adults with head and neck cancer. 30 enrolled, 27 completed.
Interventions	2 groups, zinc sulphate 50 mg zinc capsules 3 times per day starting first day of radiotherapy until 6 weeks after versus placebo. All patients access to local anaesthetic solutions and analgesic agents
Outcomes	Mucositis RTOG grading. Other reported outcomes: non-steroidal analgesics
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: randomly assigned to receive either zinc sulphate or placebo during RT" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "the placebos were empty capsules bought from the same medical firm to be identical to the zinc sulphate capsules"
Blinding (performance bias and detection bias) Carers	Unclear risk	Zinc versus placebo. Reference made to the need for a "well-designed double-blind randomized study to evaluate the reliability and effectiveness" of zinc. However, no information on blinding provided
Blinding (performance bias and detection bias) Patients	Unclear risk	Reference made to the need for a "well-designed double-blind randomized study to evaluate the reliability and effectiveness" of zinc. However, no information on blinding provided
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Reference made to the need for a "well-designed double-blind randomized study to

Ertekin 2004 (*Continued*)

		evaluate the reliability and effectiveness" of zinc. However, no information on blinding provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	30 patients randomised. 3 patients withdrew (3/15 placebo). Authors give no information about which arm patients were randomised to. 27 patients included in analysis
Selective reporting (reporting bias)	Low risk	Data presented in the text for grade of mucositis by treatment arm. Data also presented for start of mucositis (week), severity of mucositis, dose of radiotherapy at which mucositis developed (table 2), and mucositis levels 6 weeks after radiotherapy (table 3)
Other bias	Low risk	Study appears to be free of other sources of bias.

Evensen 2001

Methods	Randomised, parallel group study conducted in Norway. All randomised patients included in evaluation. Dentist involvement unclear. Recruitment September 1995-June 1998
Participants	Adults with hand and neck cancer undergoing radiotherapy. 60 enrolled, 60 completed
Interventions	2 groups, patients randomised to sucralfate mouthrinse or placebo, swish and spit, 5 times daily and same patients also received sucralfate gel to skin on one side of radiation field and placebo gel to other side of the radiation field (i.e. all patients received some sucralfate gel)
Outcomes	Mucositis & skin reaction, RTOG grading. Other reported outcomes: food intake
Notes	Funding source: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The same patients were randomly allocated to receive either Na-SOS or placebo for the oral rinsing procedure" Comment: random component not described.

Evensen 2001 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	60 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Data presented for 60 patients by treatment allocation and grade of mucositis
Other bias	Unclear risk	Difference between groups at baseline regarding tumour stage (23% sucralfate group T3/4, 53% placebo group). No P value presented

Ferretti 1988

Methods	Randomised, parallel group study conducted in USA. Unclear information on withdrawals: 1/28 control, 4/28 test. Dentist involved in study. Drop outs: 10%. Recruitment period April 1983 to March 1985. Duration: up to 90 days
Participants	Children and adults (1-51 years) with mixed blood haematological and solid cancers receiving BMT. Pretransplant chemoradiotherapy and TBI. 56 patients enrolled and 51 completed, but variable numbers of patients evaluated at each time point (24-50)
Interventions	2 groups, placebo versus chlorhexidine gluconate mouthrinse (15 cc 0.12%, 3 times per day for 30s)
Outcomes	Mucositis (clinical scale 0-3, but then dichotomised and measured at 7, 14, 25, 33, 60 & 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, febrile episodes, use of antibiotic, blood changes
Notes	Candidemia (persistant 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 and government.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "By prospective randomisation, patients were assigned in a double-blind fashion a mouthrinse containing 0.12% chlorhexidine digluconate or a control mouthrinse identical in composition but minus chlorhexidine" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Quote: "Mouthrinse use was supervised by transplant unit nursing staff for the duration of hospitalization" Comment: insufficient information to determine 'yes' or 'no'
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Quote: "mouthrinse identical in composition but without chlorhexidine" Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double Blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	56 patients randomised. 5 patients excluded. Authors give reasons for attrition/exclusion but variable numbers are evaluated at each time point and reasons for missing data are not provided
Selective reporting (reporting bias)	Unclear risk	Data presented for percentage of patients with mucositis and mean mucositis score in the form of graphs (figure 1 and figure 2). Different numbers of patients re-evaluated at each time point
Other bias	Low risk	Study appears to be free of other sources of bias.

Fidler 1996

Methods	Randomised, parallel group study conducted in USA. Unclear information on withdrawals: 1/165 total. Unlcear if dentist involved in study. Drop outs: 1%. Duration: 14 days
Participants	Adults, cancer type not given. Chemotherapy: first course 5-FU based. 165 enrolled, 164 clinical evaluation, 135 patient evaluation
Interventions	2 groups, placebo versus camomile (30 drops in 100 ml water, 3 times per day)
Outcomes	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
Notes	Mean daily mucositis scores shown graphically but no SD. All patients used ice chips 5 mins before chemotherapy and for 30 minutes in total. Patient's mucositis scores used. Funding source: government.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomised in a double-blind manner to receive a chamomile mouthwash or an identical-appearing placebo." Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double-blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double-blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	165 patients randomised. 1 patient removed due to a major protocol violation. 164 patients had evaluable physician judged mucositis scores. Patient judged mucositis scores evaluable in 135 patients

Fidler 1996 (*Continued*)

Selective reporting (reporting bias)	Low risk	Data presented for maximum severity of mucositis by grade for physician and patients judged mucositis scores (table 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Foote 1994

Methods	Randomised, parallel group, multicentre study conducted in USA and Canada. Clear information on withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration: 14 days
Participants	Adults with head and neck cancer. 52 patients were eligible, enrolled and evaluated
Interventions	2 groups, placebo versus chlorhexidine (15 ml 4 times per day for 130 s)
Outcomes	Mucositis scale 0-4 by patient and clinician at weekly intervals. Assessment used: day unclear
Notes	Funding source: pharmaceutical and government.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Following randomisation, they were randomized in a double-blind manner to receive a chlorhexidine mouthwash or a placebo mouthwash." Comment: random component not described.
Allocation concealment (selection bias)	Low risk	Quote: "only a coded bottle was communicated to the treatment centre" Comment: central allocation. Probably done.
Blinding (performance bias and detection bias) Carers	Low risk	Adequate allocation concealment. Unlikely that carers would know allocations
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double Blind". Comment: probably done.

Foote 1994 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double Blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	52 patients randomised. No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	Data presented for 52 patients for maximum mucositis severity score by grade of mucositis and intervention
Other bias	High risk	Quote: "Due to the significantly higher toxicity rates and the lack of evidence of efficacy associated with chlorhexidine, the double-blinded portion of the trial was permanently closed"

Franzen 1995

Methods	Randomised, parallel group study conducted in Sweden. Unclear information on withdrawals: 2/50 total. Unclear if dentist involved in study. Drop outs: 4%. Duration of treatment: 6 weeks (starting 2 weeks after start of radiotherapy)
Participants	Adults with head and neck cancer. 50 patients were randomised and 48 evaluated
Interventions	2 groups, placebo versus sucralfate (granules of sucralfate an alkaline aluminimum hydroxide of suphated sucrose, swish with 1 dose package 1 g dissolved in water 6 times/day)
Outcomes	Patient based assessment of mucositis on 0-3 scale, number with grades 2 or 3 reported. Assessement used: day 28. Other reported outcomes: mucosal reaction, pain, functional impairment. Mucositis evaluations from -2 to 14 weeks
Notes	Funding source: charity.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "granules of sucralfate or placebo similar in taste, colour, and consistency were dispensed randomly" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Franzen 1995 (*Continued*)

Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	50 patients randomised. 2 patients excluded from analysis. Authors give full reasons for attrition/exclusion. Numbers of patients reported in outcome assessments not reported information only given in percentages
Selective reporting (reporting bias)	Unclear risk	Data presented in a graph for mucosal reaction over time (figure 1). Figures given in percentages
Other bias	Low risk	Study appears to be free of other sources of bias.

Freytes 2004

Methods	Randomised, parallel group, multicentre study conducted in USA. Clear information on withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: 28 days after last dose of intervention
Participants	Adults with mixed cancer. BMT. 42 enrolled, randomised and evaluated
Interventions	3 groups, placebo versus repifermin 25 mug/kg and repifermin 50 mug/kg (patients received intravenous repifermin or placebo for 3 days before their autologous haematopoietic stem cell transplantation (auto-HSCT) conditioning regimen and for up to 10 days after auto-HSCT)
Outcomes	Mucositis measured 3/week until mucositis resolved using the NCI CTC mucositis toxicity scale for bone marrow transplant studies (on a scale of 0-4). Mucositis was also assessed by the OMAS scale. Assessment used: up to day 28. Other reported outcomes: severity and duration of ambient oral and oropharyngeal pain and pain on swallowing, an ability to eat score, narcotic pain medication use, adverse events incuded the frequency, severity and duration of diarrhoea
Notes	Funding source: unclear.

Freytes 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "This study was a multicentre randomised, double-blinded, placebo controlled, phase I/II study." Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	42 patients recruited. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data only presented in percentages for mucositis grades between 2 and 4 (figure 1)
Other bias	High risk	Authors highlight possible bias because of the multiplicity of conditioning regimens used.

Gandemer 2007

Methods	Randomised, parallel multicentre study conducted in France. Clear information about withdrawals: 3/73 intervention, 2/72 control. Duration: from first day of chemotherapy to 3 days after the end of chemotherapy. Recruitment conducted between March 1999 and December 2002
Participants	Children aged between 5 and 18 years old undergoing chemotherapy. Mix of diseases (osteosarcoma, Hodgkin lymphoma, acute lymphoblastic leukaemia, acute myeloblastic leukaemia, rhabdomysarcoma, lymphoma, Ewing sarcoma). all chemotherapy regimens were associated with at least a 30% rate of grade 3/4 mucositis

Gandemer 2007 (*Continued*)

Interventions	2 groups, no treatment control versus chewing gum. Patients in the chewing gum arm were asked to chew 5-6 pieces of gum per day. All patients received standard oral care (brushing with a soft toothbrush and rinsing with sodium bicarbonate)
Outcomes	Mucositis assessed daily using the WHO score and a detailed instrument designed by the authors. Other reported outcome measures: pain, abdominal disorders, use of parenteral nutrition, adverse events, infection, factors associated with severe mucositis (multivariate analysis)
Notes	Funding source: publicly funded research grant and a national clinical research grant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomised by the study randomisation centre..." Quote: "A minimization procedure was used..." Comment: minimization.
Allocation concealment (selection bias)	Low risk	Quote: "the study centres and the randomisation centres communicated by fax"
Blinding (performance bias and detection bias) Carers	High risk	Chewing gum versus no intervention. Blinding impossible.
Blinding (performance bias and detection bias) Patients	High risk	Chewing gum versus no intervention. Blinding impossible.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Chewing gum versus no intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	145 patients randomised. Primary end point (WHO score) was evaluable in 140 patients. Excluded patients equally distributed (3/73 intervention, 2/72 control) . Authors do not give reasons for withdrawals/exclusions
Selective reporting (reporting bias)	Unclear risk	Data presented in percentages for 140 patients for mucositis grades 1 and 2 combined and mucositis grades 3 and 4 combined (fig 2A)

Other bias	Low risk	Study appears to be free of other sources of bias.

Giles 2004

Methods	Randomised, parallel group, multicentre study conducted in USA between November 2001 and June 2002. Clear information on withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: 21 days
Participants	Adults and children with mixed cancer. BMT. 502 randomised and completed
Interventions	2 groups, placebo versus iseganan (patients received an oral rinse, consisting of iseganan 9 mg or placebo, to be swished/swallowed 6 times daily, for up to 21 days)
Outcomes	Mucositis assessed 3/weekly by the proportion of patients who did not develop a peak NCI CTC stomatitis grade 2 or above. Assessment used up to 21 days. Other reported outcomes: mouth pain, difficulty swallowing, incidence of ulcerative oral mucositis (UOM), opioid use, adverse events included fatigue, anxiety, sore throat, dermatitis, insomnia and erythema
Notes	Funding source: unclear. Pharmacological company provided drug and organised randomisation. Correspondence with Dr D Peterson: clinical trials with iseganan were discontinued approximately 6 years ago. Approval of the drug for oral mucositis was not obtained in the United States

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A randomised, double blind, placebo controlled study" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "all study drugs were packaged in identical white opaque plastic bottles, each containing a 5 day supply." Comment: authors do not state whether drugs were sequentially numbered. Insufficient information to determine 'yes'
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Giles 2004 (*Continued*)

Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Quote: "Patients, study personnel, and the sponsor were blinded to whether an individual patient received iseganan or placebo" Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Quote: "Patients, study personnel, and the sponsor were blinded to whether an individual patient received iseganan or placebo" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	502 patients randomised. 56% of Iseganan group and 66% of placebo group completed study. Authors give incomplete reasons for exclusion/attrition
Selective reporting (reporting bias)	Unclear risk	Data presented for percentage without mucositis, peak mucositis grade, mean mucositis grade, and incidence (percentage) of ulcerative mucositis
Other bias	Low risk	Study appears to be free of other sources of bias.

Gori 2007

Methods	Randomised, parallel multisite study conducted in Italy between October 2004 and January 2006. Clear information on withdrawals. Unclear if dentist involved in study	
Participants	Adults and children with haematological malignancies undergoing allogeneic stem cell transplantation. All patients received methotrexate (20 mg/m^2 on day +1, 5 mg/m^2 on days +3, +6 and +11). 130 patients were randomised. 8 patients were excluded. 50 patients received folinic acid rescue	
Interventions	2 groups, no treatment control versus cryotherapy (1 hour, ice chips or popsicles)	
Outcomes	Mucositis assessed daily using the WHO score. Other reported outcome measures: multivariate analysis of factors affecting mucositis development (lack of folinic acid rescue and use of TBI)	
Notes	Funding source: Italian HSCT Nurses Group.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Gori 2007 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "After giving their informed consent, patients were included in a preformed randomization list that was updated by the co-ordinating centre. Randomization was performed at the ratio of 1 patient per arm with no further stratification." Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Co-ordinating centre described in text, however, unclear who held the schedules. Therefore, there is insufficient information to determine 'yes' or 'no'
Blinding (performance bias and detection bias) Carers	High risk	Ice chips versus no intervention. Blinding impossible.
Blinding (performance bias and detection bias) Patients	High risk	Ice chips versus no intervention. Blinding impossible.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Ice chips versus no intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	130 patients were randomised. 8 patients were excluded. Authors give complete reasons for exclusions/withdrawals but do not state which arm patients were randomised to.
Selective reporting (reporting bias)	Low risk	Data presented for 122 patients by mucositis grade and arm.
Other bias	Low risk	Study appears to be free of other sources of bias.

Goyal 2009

Methods	Randomised, parallel group study conducted in India. All patients underwent oro-dental prophylaxis prior to randomisation. Recruitment conducted from July 2006 until July 2007
Participants	Adults with head and neck cancer (non-metastatic carcinoma of the oral cavity, pharynx or larynx) receiving radiotherapy. 212 patients randomised. 35 patients excluded
Interventions	Morning radiotherapy (8am-11am) versus evening radiotherapy (3pm-6pm)

Goyal 2009 (*Continued*)

Outcomes	Oral mucositis assessed weekly using RTOG instrument (0-4) for 7 weeks. Week 4 data used (table 3). Other reported outcomes: highest grade of mucositis, response to radiation, dysgeusia, dysphagia, xerostomia, skin reaction
Notes	Funding source unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "All patients were hospitalised during the course of treatment and were randomised to arm 1, receiving radiation in the morning and arm 2, receiving radiation in the evening." Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Morning versus evening radiation. Blinding impossible.
Blinding (performance bias and detection bias) Patients	High risk	Morning versus evening radiation. Blinding impossible.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "Radiation reactions were assessed weekly by a blinded observer according by RTOG criteria" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	High risk	212 patients randomised. 35 patients excluded. Authors give incomplete reasons for drop outs/exclusions and no information about which arms these patients were allocated
Selective reporting (reporting bias)	Low risk	Data presented for grade of mucositis by arm and week of treatment (table 3). Data also presented for grades I and II and grades III and IV in percentages (table 2)
Other bias	Low risk	Study appears to be free from other sources of bias.

Gujral 2001

Methods	Randomised, parallel group study conducted in India. Unclear information about withdrawals. Dentist no involved in study. Drop outs: 1%. Duration: 6 months
Participants	Adults with head and neck cancer. T3 and T4 squamous cell cancer, 100 enrolled, 99 evaluated
Interventions	2 groups, no treatment versus hydrolytic enzymes, papain 100 mg, trypsin 40 mg and chymotrypsin 40 mg. 3 tablets 3 times a day - 3 until + 5
Outcomes	RTOG/EORTC scoring. Assessment used: day 54. Other reported outcomes: dysphagia, dermatitis
Notes	No oral care except toothbrushing. Funding source: pharmaceutical

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patient randomisation was carried out by the sealed envelope method." Quote: "The patients were enrolled in chronological order. They were assigned consecutive patient numbers, and received either radiation therapy, or radiation therapy together with enzyme therapy" Comment: unclear if envelopes were shuffled. Random component not described
Allocation concealment (selection bias)	Unclear risk	Quote: "sealed envelope method." Comment: unclear whether envelopes were sequentially numbered and opaque
Blinding (performance bias and detection bias) Carers	High risk	Quote: "randomised, open trial".
Blinding (performance bias and detection bias) Patients	High risk	Quote: "randomised, open trial".
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "randomised, open trial".
Incomplete outcome data (attrition bias) All outcomes	Low risk	100 patients randomised. Outcome data given for 99 patients. 53: intervention, 46: control. 2 patients died during study 2/53 intervention. Missing patient from control group. No information given. Observed

Gujral 2001 (*Continued*)

		event risk not sufficient to have clinically relevant impact on result
Selective reporting (reporting bias)	Low risk	Data presented for 99 patients by mucositis grade (table 3). AUC data presented for 93 patients with complete data (table 4). Minimum and maximum, mean (SD) grades given for 99 patients (table 2). Data presented for time to mucositis grade 2 (table 5)
Other bias	Low risk	Study appears to be free from other sources of bias.

Haddad 2009

Methods	Randomised, parallel group, 1 site study conducted in USA. Clear information on withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration: up to 43 days
Participants	Adults with head and neck cancer. 58 patients enrolled and randomised between May 2003 and April 2006, all completed
Interventions	2 groups, no amifostine versus intravenous amifostine (500 mg/m² concomitant with 4 weekly doses of carboplatin (area under the curve, 1.5) and paclitaxel (45 mg/m²) and boost radiation 72 Gy in 42 fractions)
Outcomes	Mucositis secondary outcome as determined by Common Terminology Criteria for Adverse Events, version 3.0), assessment every 4 weeks and the worst grade recorded. Only percent of patients with grades 3 and 4 reported Other reported outcomes: xerostomia, locoregional failure, progression-free survival, overall survival (all up to 60 months), treatment related adverse events: cytokine level, feeding tubes, swallowing function, breaks in treatment, allergic reaction
Notes	Funding source: industry.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the randomisation process was centralised and managed through the Dana-Farber Cancer Institute protocol office" Comment: random component not explicit. However, setting makes adequate randomisation likely

Haddad 2009 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote: "central method of allocation". Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Radiotherapy with or without subcutaneous amifostine. No apparent blinding
Blinding (performance bias and detection bias) Patients	High risk	Radiotherapy with or without subcutaneous amifostine. No apparent blinding
Blinding (performance bias and detection bias) Outcome assessors	High risk	Radiotherapy with or without subcutaneous amifostine. No apparent blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	58 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented in percentages for number of patients experiencing grade 3 and 4 mucositis
Other bias	High risk	The study was stopped before the completion of planned accrual because IMRT was becoming the de facto standard technique in treating head and neck cancer

Hanson 1995

Methods	Randomised, parallel group multisite study conducted in the USA. Clear information about withdrawals: 0. Unclear if dentist involved in study. Duration: 5-7 weeks
Participants	Adults with head and neck cancer undergoing radiotherapy (daily fractions of 2 Gy/day, total dose: 50-70 Gy over 5-7 weeks)
Interventions	2 groups, placebo tablets or misoprostol tablets (200 μg) dissolved in 15 ml tap water. Patient asked to swish and gargle without swallowing
Outcomes	Mucositis assessed weekly using a 0-4 scale. Other reported outcome measures: plasma values of misoprostol in healthy volunteers, ability of physician to guess randomisation after blinded chart review, number of patients receiving antifungals, nasogastric tubes and parotid sparing
Notes	Funding source: pharmaceutical.
Risk of bias	

Hanson 1995 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Quote: 35 tablets containing 200 μg each of MP of 35 placebo tablets containing the vehicle alone were supplied by Searle in coded bottles" Comment: unclear if bottles were sequentially numbered.
Blinding (performance bias and detection bias) Carers	Low risk	Quote: "each patient was assigned a bottle of tablets without knowledge of the content (MP or placebo), nor did the attending physician, nursing or administrative staff knew the content or coding" Comment: probably done.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "each patient was assigned a bottle of tablets without knowledge of the content (MP or placebo), nor did the attending physician, nursing or administrative staff knew the content or coding" Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "each patient was assigned a bottle of tablets without knowledge of the content (MP or placebo), nor did the attending physician, nursing or administrative staff knew the content or coding" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	69 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for mean mucositis score over time for both hospital sites
Other bias	High risk	Significant difference seen between the 2 investigative sites in this study (1 showed an effect , the other did not). Authors have no definitive explanation but there is a suggestion that there may have been differences in the compliance with study protocol and/or the time between administration of prostagladin and the start of RT

Hartmann 2001

Methods	Randomised, parallel group study conducted in Germany. Clear information about withdrawals: 0. Unclear if dentist involved in study. Drop outs: 0%
Participants	Adults with solid cancer. 40 enrolled between August 1997 and January 1999, 40 completed
Interventions	2 groups, amifostine 910 mg/m², 15 minute IV infusion before carboplatin and ifosfamide for 3 consecutive days versus no amifostine control
Outcomes	Mucositis WHO percentage patients grade 3-4. Other reported outcomes nausea/vomiting, costs of total care, diarrhoea
Notes	Funding source: pharmaceutical.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients had given informed consent for the treatment with HD-VIC and for the randomization to pre-treatment with or without amifostine." Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Amifostine versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Patients	High risk	Amifostine versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Amifostine versus no intervention. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for median WHO grade and for percentage of patients with mucositis grades > 3 and 4
Other bias	Low risk	Study appears to be free of other sources of bias.

He 2008

Methods	Randomised, parallel group study conducted in China. Clear information about withdrawals: 0. Unclear if dentist involved in study. Drop outs: 0%. Recruitment period: unclear
Participants	Adults with oesophageal and cardiac cancer receiving chemotherapy. 48 enrolled and randomised, all completed
Interventions	2 groups, 20 g glutamine daily versus a placebo (compound amino acid) given by 'injection' possibly into parenteral nutrition solution
Outcomes	Mucositis severity evaluated using 0-4 scale NCI CTCAE criteria, grade 0, 1, 2 versus grade 3, 4, nausea/vomiting, diarrhoea, leucopenia, weight loss
Notes	Funding source: government. All above information obtained from Chinese translation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote "randomization table". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Quote "randomization table". Comment: method of concealment unclear.
Blinding (performance bias and detection bias) Carers	Unclear risk	Parenteral amino acid solution with or without glutamine. No apparent blinding
Blinding (performance bias and detection bias) Patients	Unclear risk	Parenteral amino acid solution with or without glutamine. No apparent blinding
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Parenteral amino acid solution with or without glutamine. No apparent blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	48 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for number of patients with grades 0-2 mucositis and grades 3-4 mucositis for both arms
Other bias	High risk	ROB assessed from a translation.

Hu 2005

Methods	Randomised, parallel group study conducted in China. Clear information about withdrawals: 0. Unclear if dentist involved in study. Drop outs: 0%
Participants	Adults with head and neck cancer receiving radiotherapy. 140 enrolled and randomised, all completed
Interventions	2 groups, Shenqi Fanghou recipe (author named) Chinese herb decoction containing 22 specifically selected herbs such as codonopsis pilosula 30 g, raidx astragali 30 g, Indian buead 30 g, etc. altogether 406 g as a dosage for a day. All the herbs were put into water for boiling then removing the herbs and 400 ml of solution obtained. The patients were asked to intake the solution orally, 200 ml a time and twice a day. No treatment control. All patients gargled with 2% lidocaine before meals and at night
Outcomes	Mucositis severity evaluated using 0-4 scale and the highest grade throughout radiotherapy course reported. Unclear how often this was measured but results reported by grade of mucositis
Notes	Funding source: unclear. All above information obtained from Chinese translation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised".
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Shenqi Fanghou recipe versus no treatment. No apparent blinding
Blinding (performance bias and detection bias) Patients	High risk	Shenqi Fanghou recipe versus no treatment. No apparent blinding
Blinding (performance bias and detection bias) Outcome assessors	High risk	Shenqi Fanghou recipe versus no treatment. No apparent blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	140 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Data presented for 140 patients by grade and treatment arm.
Other bias	High risk	Risk of bias assessed from translation.

Huang 2000

Methods	Randomised, parallel group study conducted in Taiwan. Clear information about withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: beginning of radiation treatment until 25 factions (5 weeks). Recruitment July 1997 to June 1998
Participants	Adults with head and neck cancer. 17 patients were enrolled and evaluated
Interventions	2 groups, placebo (30 ml saline) versus glutamine (2 g in 30 ml saline, swish 30 ml 3 mins then expectorate)
Outcomes	Clinicians assessed subjective mucositis on 0-4 scale and objective RTOG/EORTC 0-4 scale. WHO step of analgesic drugs. Assessment used: day unclear
Notes	Subjective mucositis scale used. Funding source: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were sequentially randomised to two treatment arms" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "single blind randomised study". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "due to manpower problems, not all physicians who evaluated patients were blind to test solutions" Comment: assessors not blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	17 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Maximum grade of mucositis by grade and treatment arm (table 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Huang 2003

Methods	Randomised, parallel group study conducted in China. Clear information on withdrawals. Unclear whether dentist involved in study. Drop outs: 0%. Duration: average radiotherapy 50 days
Participants	Adults with head and neck cancer treated with chemotherapy cisplatin (DDP 30 mg/m²) with concomitant radiotherapy. 101 patients recruited and evaluated
Interventions	2 groups, Dobell's solution (unclear what this is) gargled 5-8 times daily versus Chinese medicine (sucked and swallowed) 6 times from first to sixth week of radiotherapy. Patients received either Chinese medicine or Dobell's solution 5-8 times daily. The decoction is made as solution by cooking the 11 herbs together with water. Doses of the herbs for 1 day are: coastal glehnia 30 g, dwarf lilyturf tuber root 30 g, rehmannia dried root 30 g, figwort rood 15 g, spreading hedyotis herb 30 g, belamcauda rhizome 15 g, platycodon root 15 g, shinyleaf pricklyoash root 15 g, honeysuckle flower 15 g, licorice root 3 g, lalanggrass rhizome 20 g. The authors follow theoretical principles of Chinese medicine: treatment should be modified in adapting the changes of the diagnosis. So, if the patients with symptoms of rhinorrhagia or blood clot in the sputum, adding hairy vein agrimony herb 20 g, hyacinth bletilla tuber 15 g; with nausea and vomiting adding red ochre 15 g, magnolis bark of Sichuan 15 g, bamboo shaving 15 g; with obstruction of the nose, adding sibirian cocklebur fruit 15 g, magnolia flower 15 g; with malaise and poor appetite, adding pseudostellaria root 30 g, bighead atractylodes rhizome 15 g, malt 30 g, millet sprout 30 g; with the tongue in dark pink colour, adding root of red rooted salvia 15 g, powder of notoginsen 3 g
Outcomes	Mucositis assessed according to acute oropharyngeal mucositis grade on a 0-4 scale
Notes	Pharmacological company provided drug and organised randomisation. This information was provided by Chinese translation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation were randomly assigned by random numbers generated from random number table"
Allocation concealment (selection bias)	Unclear risk	Comment: random number table.
Blinding (performance bias and detection bias) Carers	High risk	Difference between intervention and control in the mode of application (gargle versus suck and swallow). Blinding impossible.
Blinding (performance bias and detection bias) Patients	High risk	Difference between intervention and control in the mode of application (gargle versus suck and swallow). Blinding impossible.

Huang 2003 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Incomplete outcome data (attrition bias) All outcomes	Low risk	101 patients randomised. No withdrawals/ exclusions.
Selective reporting (reporting bias)	Low risk	Data presented for 101 patients for mucositis incidence by grade and treatment
Other bias	High risk	Risk of bias assessed from a translation.

Ifrah 1999

Methods	Randomised, parallel group study conducted in France. Unclear information about drop outs. Unclear if dentist involved in study
Participants	Adults with blood cancer. 67 enrolled and randomised between November 1990 and April 1992, results given on 64
Interventions	2 groups, rGM-CSF 5 ug/kg as a 6 hour IV infusion versus placebo
Outcomes	WHO mucositis score (> 3).
Notes	Funding source: none.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "At admission, patients were randomised to receive either rGM-CSF or a placebo 24 hours after induction treatment was completed." Quote: "the randomisation sequences were generated by the co-ordinating centre and were balanced with each centre"
Allocation concealment (selection bias)	Unclear risk	Quote: "the randomisation sequences were generated by the co-ordinating centre and were balanced with each centre" Comment: unclear if allocation remained with the co-ordinating centre. Insufficient information to determine 'yes' or 'no'
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Ifrah 1999 (*Continued*)

Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	67 patients randomised. 3 patients withdrew (1 patient was ineligible, 2 patients withdrawn due to major dose errors). Authors give full reasons for attrition/exclusion but do not state which arms patients were randomised too
Selective reporting (reporting bias)	Unclear risk	Data presented for mucositis grade > 3 (WHO score) (table 2) and duration of mucositis grade > 2 (median values in days) (table 4) for patients receiving autologous transplantation
Other bias	High risk	Patients randomised to the rGM-CSF arm were older (median age 36 years versus 28 years, P = 0.04) More patients randomised to the rGM-CSF arm had Philadelphia chromosome, P = 0.026

Jebb 1994

Methods	Randomised, cross-over study conducted in UK. Unclear information about withdrawals: 11/28 in total. Dentist not involved in study. recruitment period: not stated. Drop outs: 39%. Duration: (1st part) 8 days.
Participants	Adults with gastrointestinal cancer undergoing 5-FU & folic acid daily for 5 days and repeated 4 weeks from start. 28 patients enrolled and 17 completed 2 cycles
Interventions	2 groups, glucose polymer (Polycal) (described as placebo) versus glutamine (16 mg daily divided into 4 equal doses and dissolved in 150 ml water before consumption), swish and swallow
Outcomes	WHO mucositis score, mouth comfort, ease of eating. Assessment used: day 8
Notes	Funding source: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Jebb 1994 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to receive either glutamine or placebo with the first cycle of treatment and the alternative supplement with cycle 2, such that each patient could act as his or her control" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients and investigator were unaware of the randomisation order for each subject" Comment: insufficient information to determine 'yes' or 'no'
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	High risk	28 patients randomised. Paired outcome data available for 17 patients who completed 2 courses of treatment. Authors give full reasons for attrition/exclusion. However, there is the potential for the overall estimate to be reversed if excluded patients included
Selective reporting (reporting bias)	Low risk	Data presented for maximum WHO mucositis grade for 17 patients (34 scores) (figure 1a and figure 1b)
Other bias	Low risk	Study appears to be free of other sources of bias.

Katano 1995

Methods	Randomised, parallel group study conducted in Japan. Clear information about withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration: administration ceased when leukocyte exceeded 8000/mm^3
Participants	Adults with solid (breast cancer). 14 patients enrolled and evaluated. Recruitment January 1992 to December 1996

Katano 1995 (*Continued*)

Interventions	2 groups, no treatment versus G-CSF (by injection 125 ug).
Outcomes	WHO mucositis score (0-4) by clinician. Other reported outcomes: alopecia, fever. Assessment used: day 8
Notes	Funding source: pharmaceutical supply product.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "they were randomised into two groups of 7 patients each" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	G-CSF versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Patients	High risk	G-CSF versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	High risk	G-CSF versus no intervention. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for incidence and duration (days) of mucositis
Other bias	Low risk	Study appears to be free of other sources of bias.

Kaul 1999

Methods	Randomised, parallel group study conducted in India. Unclear information about withdrawals. Dentist not involved in study. Drop outs unclear. Duration unclear
Participants	Adults with head and neck cancer radiotherapy 50-60 Gy/5-6 weeks. 50 patients enrolled

Interventions	2 groups, no treatment control versus wobe-mugos enzyme preparation 3 tablets/day 3 days prior to RT until 1 week after
Outcomes	Mucositis. Assessment used: day 28. Other reported outcomes: xerostomia, skin changes, dysphagia, hospitalisation
Notes	Funding source: none.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A prospective randomised phase III clinical trial". Quote: "A randomisation of 50 patients fulfilling inclusion criteria" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	No intervention versus 9 tablets. No apparent blinding.
Blinding (performance bias and detection bias) Patients	High risk	No intervention versus 9 tablets. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	High risk	No intervention versus 9 tablets. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	50 patients randomised. 1 patient died during study. 69.4% of patients completed the study without a treatment gap. However, authors presented data for 25 patients (50%) at week 11 of the study. Authors do not give full reasons for attrition/exclusion
Selective reporting (reporting bias)	Unclear risk	Data presented for oral mucositis by grade for radiotherapy and radiotherapy plus wobe-mugos for 11 weeks of treatment. Data only presented for 50% of sample at week 11

Other bias	Low risk	Study appears to be free of other sources of bias.

Kazemian 2009

Methods	Randomised, parallel group study conducted in Iran between 2004 and 2005. Full information given on withdrawals. Dentist involved in study. Drop outs: 19%
Participants	Adults with head and neck cancer receiving radiotherapy. 100 enrolled in study, 81 were evaluated, 39 in the benzydamine group and 42 in the placebo group
Interventions	2 groups, placebo versus benzydamine (0.15 benzydamine oral rinse). Participants rinsed with 15 ml for 2 minutes, 4 times per day from the first day of radiotherapy treatment to the end
Outcomes	Assessment on the RTOG grading system for oral mucositis, assessment carried out weekly. Other reported outcomes: effects of smoking, effects of chemoradiotherapy
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "one hundred patients were randomised into this study" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	100 patients randomised. 81 patients included in the analysis. 19 cases excluded. Exclusions equally distributed. 17/19 stopped due to side effects. Authors pro-

Kazemian 2009 (*Continued*)

		vide full reasons for withdrawals/drop outs
Selective reporting (reporting bias)	Unclear risk	Data presented for grade > 3 mucositis (in text).
Other bias	Low risk	Study appears to be free of other sources of bias.

Koukourakis 2000

Methods	Randomised, parallel group study conducted in Greece. Unclear information on withdrawals 0/20 control, 1/20 test. Unclear if dentist involved in study. Drop outs: 3%. Duration 6-7 weeks
Participants	Adults with 3 cancer types: thoracic, pelvic, RT postoperative or inoperable dose 64-70 Gy. 140 patients enrolled between July 1997 and May 1999, 130 completed
Interventions	2 groups, no treatment control versus amifostine 500 mg daily before RT
Outcomes	Mucositis 0-4 scale combined categories. Assessment used: unclear. Other reported outcomes RT delay, side effects
Notes	Patients selected from other types of cancer because mucositis data available. Funding source: government & pharmaceutical

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned to undergo radiotherapy or radiotherapy supported with subcutaneous administration of Amifostine, according to a table of random numbers (0 V 1)." Comment: authors used random number table.
Allocation concealment (selection bias)	High risk	Comment: open random table.
Blinding (performance bias and detection bias) Carers	High risk	Amifostine versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Patients	High risk	Amifostine versus no intervention. No apparent blinding.

Koukourakis 2000 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	High risk	Amifostine versus no intervention. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	140 patients randomised. Interruption of treatment in 10 patients. 10/70 amifostine. Mucositis data presented for 130 patients
Selective reporting (reporting bias)	Unclear risk	Data presented for 130 patients for grades 0/1, grade 2, and grade 3/4 (table 4)
Other bias	Low risk	Study appears to be free of other sources of bias.

Labar 1993

Methods	Randomised, parallel group study conducted in Croatia. Clear information about withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: +7 to day +21
Participants	Children and adults (5-43 years) with blood cancers, undergoing BMT. 60 patients eligible, enrolled and evaluated
Interventions	2 groups, placebo versus prostaglandin E2 (0.5 mg 3 times per day)
Outcomes	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 SD given. Assessment used: day 35. Other reported outcomes: HSV infection, microbiology, vomiting, diarrhoea, fever, death, GVHD (c)
Notes	Funding source: none.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the patients were randomised to receive either prophylactic regimen A or B according to the Pocock and Simon method" Comment: minimization.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Labar 1993 (*Continued*)

Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	60 patients randomised. Authors give outcome data in percentages making it difficult to assess the possibility of incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Data presented in percentages in a piechart for grades I and II vs grades III and IV (figure 1) and severity of OM over time (figure 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Leborgne 1997

Methods	Randomised, parallel group study conducted in Uruguay. Unclear information about withdrawals. Unclear whether dentist involved in study. Drop outs: 4%. Duration 90 days
Participants	Adults with head and neck cancer radical RT. 69 enrolled, 66 completed
Interventions	2 groups, placebo versus prednisone 40 mg once daily through day 28 reduced dose to day 43
Outcomes	Mucositis WHO. Assessment used: unclear. Other reported outcomes: duration of treatment, treatment interruptions, parenteral nutrition, hospital stay, weight loss, locoregional control, survival
Notes	Funding source: not stated. Mucositis data for all grades of severity obtained after writing to authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "69 patients were randomized". Comment: random component not described.

Leborgne 1997 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote: "The codes were broken after the mucosal reactions in the last patient were scored." Comment: insufficient information to determine 'yes' or 'no'
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	69 patients randomised. 3 patients were excluded due to major protocol violations. Authors give full reasons for exclusions but do not state which arms patients were randomised to
Selective reporting (reporting bias)	Low risk	Mucositis data for all grades of severity obtained after writing to authors
Other bias	High risk	Baseline differences: significantly more patients in the treatment arm had stage 3 disease compared to placebo (P = 0.02)

Li 2006

Methods	Randomised, parallel group study conducted in China. Clear information about withdrawals: 1 from glutamine group. Unclear if dentist involved in study. Drop outs: 2%. Recruitment March 2001 to December 2002
Participants	Adults with breast cancer receiving 5-FU chemotherapy. 60 enrolled and randomised, 59 completed
Interventions	2 groups, 30 received 30 g oral glutamine per day for 12 days prior to chemotherapy, 29 received placebo
Outcomes	Mucositis severity evaluated using 0-4 scale (NCI CTCAE) (grade 3-4). Other reported outcomes: intestinal permeability, intestinal toxicity, plasma glutamine levels
Notes	Funding source: government.

Li 2006 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible study patients were randomly assigned to a placebo (n = 30) or a glutamine group (n = 30)." Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Unclear risk	Glutamine versus placebo (glycerine).
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Glutamine versus placebo (glycerine).
Incomplete outcome data (attrition bias) All outcomes	Low risk	60 patients randomised. 1 patient (1/30 glutamine) excluded from analysis due to lack of toxicity data
Selective reporting (reporting bias)	Unclear risk	Data presented in a graph for grade of stomatitis (grade 0, grade 1-2, grade 3-4) by arm in percentages
Other bias	Low risk	Study appears to be free of other sources of bias.

Lievens 1998

Methods	Randomised, parallel group study conducted in Belgium. Clear information about withdrawals: 19 (12 sucralfate and 7 placebo). Unclear if dentist involved in study. Duration: 25-33 days (entire duration of therapy)
Participants	102 adults with head and neck cancers receiving radiotherapy (5 fractions per week, doses ranged from 55 Gy in 25 daily fractions of 2.2 Gy to 66 Gy in 33 daily fractions of 2 Gy)
Interventions	2 groups, placebo versus sucralfate (1 g 6 times daily).

Lievens 1998 (*Continued*)

Outcomes	Mucositis scored once weekly using 0-6 scale. Other reported outcome measures: subjective intolerance to radiotherapy treatment, dysphagia, nausea, dermatitis, weight loss, side effects
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomised". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	102 patients randomised. 19 patients withdrew (12 sucralfate, 7 placebo)
Selective reporting (reporting bias)	Unclear risk	Data presented for mean peak mucositis.
Other bias	Low risk	Study appears to be free from other sources of bias.

Lilleby 2006

Methods	Randomised, parallel group study conducted in USA. Clear information on withdrawals: 1 in saline group withdrew consent because wanted ice chips. Dentist not involved in study. Drop outs: 2%. Duration: -2 to 28 days post-transplant
Participants	Adults with blood cancer - multiple myeloma scheduled to receive melphalan 200 mg/m² followed by BMT- autologous stem cell transplantation (ASCT). 41 enrolled and randomised, 40 completed

Interventions	2 groups, room temperature normal saline rinse versus ice chips (oral cryotherapy) 30 minutes before and 6 hours after high-dose therapy
Outcomes	Mucositis was assessed as part of routine care using the NCI CTC grades 0-4. Assessment used: -2 to 28 days. Other reported outcomes: days of total parenteral nutrition (TNP) , narcotic use, hospitalisation, weight loss and resumption of oral caloric intake for 28 days after transplant
Notes	Funding source: charity.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to receive either ice-chips or room temperature normal saline rinses." Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Ice chips versus saline. Blinding impossible.
Blinding (performance bias and detection bias) Patients	High risk	Ice chips versus saline. Blinding impossible.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Ice chips versus saline. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	41 patients randomised. 1 patient withdrew: 1/20 saline group. Authors give reasons for attrition/ exclusion
Selective reporting (reporting bias)	Low risk	Data presented for all patients by arm and mucositis grade (table 3)
Other bias	Low risk	Study appears to be free of other sources of bias.

Lin 2006

Methods	Randomised, parallel, multisite study conducted in Taiwan. Clear information on withdrawals: 3 (2 placebo, 1 intervention). Unclear if dentist involved in study. Recruitment conducted from January 2003 until August 2004. Duration: during radiotherapy treatment (approximately 2 months)
Participants	Adults with head and neck cancers receiving radiotherapy (180 cGy to 200 cGy in 5 weekly fractions) with or without concurrent chemotherapy (no extra information). 100 randomised, 97 completed
Interventions	2 groups, soya bean oil placebo versus oral zinc (25 mg Pro-Z) (3 capsules a day)
Outcomes	Mucositis assessed weekly using the RTOG criteria for acute morbidity. Other reported outcome measures: dermatitis, weight loss, interruption of radiotherapy, adverse events
Notes	Funding source: Chi-Mei Foundation Medical Centre.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Blocked randomisation was used for all subjects to achieve balanced assignment. We adapted the RV.Uniform (0,1) function in SPSS for windows to generate random numbers and to assign distinct random permuted blocks to subjects" Comment: computer generated randomisation.
Allocation concealment (selection bias)	Unclear risk	Quote: "The drug contents were not revealed, even to the principal investigator until the end of the experiment" Comment: insufficient information to determine 'yes' or 'no'
Blinding (performance bias and detection bias) Carers	Unclear risk	Comment: authors state that serum zinc levels were checked biweekly, staff who checked these levels would presumably have knowledge of allocation
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Comment: authors state that serum zinc levels were checked biweekly, staff who checked these levels would presumably have knowledge of allocation

Lin 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	100 patients randomised. 3 patients dropped out (1/50 intervention, 2/50 placebo group). Authors give reasons for withdrawals/drop outs
Selective reporting (reporting bias)	Unclear risk	Data presented for time to grade 2 and 3 mucositis in text. Mean scores for mucositis plotted over time by treatment arm in fig 3
Other bias	Low risk	Study appears to be free from other sources of bias.

Lockhart 2005

Methods	Randomised, parallel group study conducted in USA. Clear information on withdrawals: none. Unclear whether dentist involved in study. Drop outs: 0%. Duration: unclear
Participants	Adults with mixed cancer. BMT - autologous blood stem cell transplant (ABSCT). 36 enrolled, randomised and completed
Interventions	2 groups, placebo versus pilocarpine (patients were randomised to receive a 5 mg tablet of pilocarpine, or a placebo, during and following chemotherapy)
Outcomes	Mucositis assessed every other day using the WHO mucositis score and the authors' own developed data entry forms to capture subjective and objective data, including toxicity criteria. This new tool is a highly modified version of the Southwest Oncology Group (SWOG) toxicity scale. We used the highest score mucositis score recorded, supplied by author. Assessment used: up to day 10. Other reported outcomes: problems with nutrition, oral infection, use of narcotics for mucosal pain, problems with oral hygiene, gingival bleeding, eating, speaking and sleeping (ordinal variables), pain at rest or with swallowing, mouth dryness (VAS scale)
Notes	Funding source: charity/foundation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were stratified according to initial diagnosis and randomized by computer generated numbering scheme to receive either pilocarpine or an identical-appearing placebo" Comment: computer generated randomisation.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Lockhart 2005 (*Continued*)

Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	36 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for incidence and duration of oral mucositis, gingival mucositis and oropharyngeal mucositis (days) (Table 3) ; highest grade of mucositis by treatment arms, average mucositis score between days 4 and 8 by treatment arm and average mucositis score between days 6 and 8 (separated into oral, gingival and oropharyngeal) (fig 1).
Other bias	Low risk	Study appears to be free of other sources of bias.

Loprinzi 1990

Methods	Randomised cross-over trial conducted in USA. Clear information on withdrawals: none. Dentist was not involved. Drop outs: 0%. Duration: 5 days
Participants	Adults with colorectal cancer receiving first 5 day course of 5-FU. 77 patients enrolled, and completed 1st period, only 20 completed 2nd period
Interventions	2 groups, placebo versus allupurinol 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)
Outcomes	Mucositis (physician and patient scales 0-4). Assessed used: day 30
Notes	Data cross-tabulated in a form suitable for meta-analysis provided by authors. Funding source: none.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Loprinzi 1990 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "a dynamic randomization procedure was utilized for assigning patients to initially receive either the allopurinol or the placebo mouthwash." Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	77 patients recruited. Data from all patients included in analysis
Selective reporting (reporting bias)	Low risk	Data presented for 77 patients for physician judged mucositis (table 2) and 71 patients for patient judged mucositis grade (table 3)
Other bias	High risk	Study aimed to recruit 120 patients but was terminated early after 77 patients were recruited after the power calculation was rerun and the results found to favour the intervention

Madan 2008

Methods	Randomised, parallel study conducted in India. Clear information on withdrawals: 4. Unclear if dentist involved in study. Duration: 6 weeks
Participants	Adults with head and neck cancer receiving radiotherapy (2 Gy daily dose, total dose 60 Gy)
Interventions	4 groups, 0.12% chlorhexidine versus 1% povidone-iodine versus salt/sodium bicarbonate versus plain water. All mouthwashes given in doses of 10 ml twice a day for 6 weeks
Outcomes	Mucositis assessed weekly using WHO scale. Other reported outcome measures: none

Notes	Funding source: Manipal University, India.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned". Comment: random component not described.
Allocation concealment (selection bias)	Low risk	Quote: "the mouthwashes were numbered randomly from 1 to 80 by the mouthwash manufacturer. The coding was done by the manufacturer and was known only to him. It was revealed to the investigator only at the end of the study. Mouthwashes were dispensed in identical 500 ml coded glass bottles" Comment: sequentially numbered drugs containers of identical appearance
Blinding (performance bias and detection bias) Carers	Low risk	Double blind study with adequate allocation concealment. Unlikely that carers would have knowledge of allocations
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	80 patients randomised. 4 patients dropped out (1/20 chlorhexidine group, 1/20 povidone, 2/20 salt and bicarbonate). Authors give reasons for withdrawals
Selective reporting (reporting bias)	Unclear risk	Data presented for mean mucositis scores by arm by week of treatment (fig 2 and table 2)
Other bias	Low risk	Study appears to be free from other sources of bias.

Mahood 1991

Methods	Randomised, cross-over study conducted in USA. 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
Participants	Adults mostly over 40 years with cancer of the colon (solid cancer). Chemotherapy first 5 day course of 5-FU. 95 patients eligible and enrolled and 93 completed first cycle, however, only 82 patients assessed mucositis
Interventions	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
Outcomes	Mucositis (physician & patients scales 0-4) and historical 1 month after treatment. Assessment used: day 28
Notes	Data cross-tabulated in a form suitable for meta-analysis provided by authors. Funding source: government.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "prior to therapy, patients were stratified by age and whether or not they had denture. They were then randomised to a control arm or to receive cryotherapy" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Ice chips versus saline. Blinding impossible.
Blinding (performance bias and detection bias) Patients	High risk	Ice chips versus saline. Blinding impossible.
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Quote: "the attending physician who judged the mucositis grade was frequently not aware of whether the patient had received cryotherapy or not" Comment: insufficient information to determine 'yes' or 'no'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	95 patients randomised. 2 patients not included in final analysis due to lack of data. Authors do not state which arms missing

Mahood 1991 (*Continued*)

		were randomised. Patient judged mucositis scores collected from 85 patients. Authors do not state to which arms missing were randomised
Selective reporting (reporting bias)	Low risk	Physician judged mucositis scales presented for 93 patients (table 2). Patient judged mucositis scales presented for 82 patients (table 3)
Other bias	Low risk	Study appears to be free of other sources of bias.

Makkonen 1994

Methods	Randomised, parallel group study conducted in Finland. Clear information about withdrawals: none mentioned. Dentist involved in study. Drop outs: 0%. Duration: during therapy (9 weeks). Recruitment November 1989 to December 1991
Participants	Adults with head and neck cancer. 40 patients eligible, enrolled and evaluated
Interventions	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
Outcomes	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 anaesthetic mouthwash, radiotherapy interrupted, toxicity
Notes	Visit at week 4 taken. Antifungal agents given to 29 patients during study. Funding source: government.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The sealed envelope method was used in randomization, and the envelopes were opened only after all clinical information for each patient had been collected." Comment: unclear if envelopes were shuffled. Random component not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "All drugs prepared by the manufacturer, 1 g sucralfate or identically looking placebo granules were sealed in coded paper bags" Sealed envelope method of randomisation.

Makkonen 1994 (*Continued*)

		However, authors do not state whether envelopes or bags were sequentially numbered
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients recruited. Authors give mucositis data for 40 patients after 3 weeks of treatment
Selective reporting (reporting bias)	Low risk	Data presented for grade of mucositis at week 3 for all patients (text), and for percentage of patients with radiation mucositis in each group at each evaluation visit (fig 1).
Other bias	High risk	Significant differences between the group for sex (P = 0.05) and age (P = 0.04) of patients at randomisation. Both have been suggested as independent variables for mucositis severity 3 patients had a buccal mucosa resection as part of their treatment. Authors provide no information about allocation of these patients. Dentate patients (10 sucralfate & 6 placebo) also received weekly fluoride treatments

Makkonen 2000

Methods	Randomised, parallel group study conducted in Finland. Clear information about withdrawals: none. Dentist involved in study. Drop outs: 0%. Duration: during therapy (9 weeks)
Participants	Adults with head and neck cancer. 40 patients eligible, enrolled between November 1994 and August 1996, all were evaluated
Interventions	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)

Outcomes	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
Notes	All patients used sucralfate suspension 1 g 6 times daily. Funding source: pharmaceutical.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "after obtaining an oral informed consent, assignment to the treatment groups were carried out via a phone call to the randomisation centre at the Finnish Cancer registry, Helsinki." Comment: random component not explicit. However, setting makes adequate randomisation likely
Allocation concealment (selection bias)	Low risk	Quote: "after obtaining an oral informed consent, assignment to the treatment groups were carried out via a phone call to the randomisation centre at the Finnish Cancer registry, Helsinki." Comment: central method of allocation.
Blinding (performance bias and detection bias) Carers	High risk	Quote: "open, prospective, randomised study". Comment: no blinding.
Blinding (performance bias and detection bias) Patients	High risk	Quote: "open, prospective, randomised study". Comment: no blinding.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "open, prospective, randomised study". Comment: no blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients recruited. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented in graphs showing percentages of patients with mucositis (fig 1) and mucosal pain (fig 2). Figures given in the text for percentage of patients with mucositis at weeks 1 and 3

Makkonen 2000 (*Continued*)

Other bias	Low risk	Study appears to be free of other sources of bias.

McAleese 2006

Methods	Randomised, parallel group study single centre study conducted in the UK. Clear information about withdrawals: 2/29. Unclear if dentist involved in study. Drop outs: 7%. Duration: 10 weeks
Participants	Adults with head and neck cancer to be treated with radiotherapy. 29 patients eligible, enrolled between September 1997 and October 2000. 27 patients evaluated
Interventions	2 groups, GM-CSF at dose of 150 ug subcutaneous injection once daily for 14 days beginning at the end of second week of radiotherapy. Compared to no treatment
Outcomes	RTOG rating for mucositis on 0-4 scale.
Notes	Maximum value of mucositis taken. Funding unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "29 patients agreed to enter and were randomly assigned to the active or control arms." Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	High risk	Quote: "A placebo injection was not used because it was not considered ethically justifiable" Comment: GM-CSF versus no intervention.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "At each visit one of two independent observers, blinded to group allocation, scored mucositis by the RTOG system?"

McAleese 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	29 patients recruited. 2 patients withdrew (2/15 intervention group). Authors give full reasons for exclusions and withdrawals. ITT analysis performed. Mucositis data given for 29 patients
Selective reporting (reporting bias)	Low risk	Maximum mucositis grades given for 29 patients by arm in text. Data also presented for the proportion of patients with each grade by arm in graphs (fig 1 and fig 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

McGaw 1985

Methods	Randomised, parallel group single site study conducted in Canada. Dentist involved in study. Drop outs: 0%. Duration: 28 days. No enrolment dates
Participants	16 patients with acute myeloblative leukaemia aged between 17 and 54 years old. All patients received conditioning with cytosine-arabinoside (200 mg/m^2 daily for 5 days) , adriamycin (40 mg/m^2 on day 1 and 2) and amsacrine (100 mg/m^2 daily for 5 days) chemotherapy.
Interventions	2 groups, intervention group received 10 ml of 0.1% aqueous solution of chlorhexidine gluconate (corsodyl), placebo group received a identically coloured and flavoured solution. Both groups rinsed twice daily for 2 minutes
Outcomes	Hickey instrument used (0-3 scale). Other outcome measures: dental plaque scores, gingivitis scores, numbers of patients developing candidiasis, number of patients requiring antibiotics, average number of febrile days, level of tooth staining and discolouration
Notes	Funding source: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients randomised into two experimental groups". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.

McGaw 1985 (*Continued*)

Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 patients randomised. No incomplete outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for mean mucositis score by week for both study arms
Other bias	Low risk	Study appears to be free from other sources of bias.

Meropol 2003

Methods	Randomised, parallel group, multicentre study conducted in USA. Clear information about withdrawals: 0. Dentist not involved in study. Drop outs: 0% Duration: 28 days
Participants	Adults with solid cancer treated with 5-FU. Patients enrolled, 81 completed
Interventions	2 groups, KGF IV injection patient cohorts treated with escalating doses of KGF 1,10, 20, 40, 60 and 80 micrograms/kg per day versus placebo control
Outcomes	Mucositis WHO grading evaluated by examination on day 1, 4, 8, 15 and 28. Other reported outcomes: nausea, vomiting, blood changes
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "This study was a multicentre, randomized, double blinded, placebo controlled, phase I study" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Meropol 2003 (*Continued*)

Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	81 patients recruited. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data only presented in graphical form for incidence of grade 2 to 4 mucositis (as percentage), duration of mucositis (days) and patient reports of mucositis. Full data not presented
Other bias	Low risk	Study appears to be free of other sources of bias.

Mills 1988

Methods	Randomised, parallel group study conducted in South Africa. Clear information about withdrawals: 0. Dentist not involved in study. Drop outs: 0%. Duration: unclear
Participants	Adults with head and neck cancer. 10 enrolled, 10 completed.
Interventions	2 groups, beta carotene (250 mg/day for 21 days, 75 mg daily after this) versus no treatment control
Outcomes	Mucositis.
Notes	Funding source: pharmaceutical.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomised to receive standard diet with supplemental beta carotene (study patients) or standard diet only with no placebo (control patients)." Comment: random component not described.

Mills 1988 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Beta-carotene versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Patients	High risk	Beta-carotene versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Beta-carotene versus no intervention. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Data presented by mucositis grade by weeks of treatment (table 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Motallebnejad 2008

Methods	Randomised, parallel group study conducted in Iran. Clear information about withdrawals. Unclear if dentist involved in study. Duration unclear (5-6 weeks?)
Participants	Adults with head and neck cancer receiving radiotherapy (1.8 Gy to 2 Gy per day, total dose 50-60 Gy)
Interventions	2 groups, saline (20 ml saline 0.09% before and after radiotherapy) versus honey (20 ml pure honey, 15 minutes before and 15 minutes after radiotherapy, and 6 hours after radiotherapy)
Outcomes	Mucositis assessed using the OMAS instrument weekly. Other reported outcomes: weight loss
Notes	Funding source: university.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Comment: random component not described.

Motallebnejad 2008 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	High risk	Honey versus saline. Single blind study.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "evaluator was blinded to the group assignments of the patients" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for mean rank of OMAS (table 1), end of week OMAS score (fig 1) and change in OMAS score (fig 2) for both arms of the study
Other bias	Low risk	Study appears to be free from other sources of bias.

Nemunaitis 1995

Methods	Randomised, parallel group, multicentre study conducted in USA and Canada. Clear information about withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration: 1 year
Participants	Adults with mixed cancer receiving BMT, chemotherapy cyclosporine & prednisolone. 109 patients enrolled between November 1990 and July 1993. 109 completed
Interventions	2 groups, placebo versus RhGM-CSF (human granulocyte macrophage colony-stimulating factor) 250 ug/m²/day IV day 0-20
Outcomes	Mucositis scored by nurse 3 grades (categorised according to WHO criteria for analysis) . Assessment used: day 28. Other reported outcomes: infection, anorexia, diarrhoea, hypertension, stomatitis. Mucositis reported on all 109 patients
Notes	Funding source: pharmaceutical.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Nemunaitis 1995 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "Assignment to treatment was made via a randomisation schema prepared by Almedica Corporation (Waldwick, NJ)" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "Blinded numbered vials containing placebo or rhGM-CSF were provided to each participating centre" Comment: unclear whether these vials were sequentially numbered
Blinding (performance bias and detection bias) Carers	Low risk	Quote: "The pharmacists, principal investigators, patients, support care personnel and sponsoring company were blinded to the study medication for the entire course of the study"
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "The pharmacists, principal investigators, patients, support care personnel and sponsoring company were blinded to the study medication for the entire course of the study"
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "The pharmacists, principal investigators, patients, support care personnel and sponsoring company were blinded to the study medication for the entire course of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	109 patients recruited. 21 patients withdrew (13/53 intervention, 8/56 placebo). Authors provide full reasons for drop outs/withdrawals. All patients included in efficacy and toxicity analyses
Selective reporting (reporting bias)	Unclear risk	Data given in the text for percentage of patients with > grade 2 mucositis and grade 3/4 mucositis
Other bias	High risk	5 patients in placebo arm also received cytokines off study during the first 42 days post-transplant

Nottage 2003

Methods	Randomised, parallel group study conducted in Canada. Clear information about withdrawals, 1 placebo. Dentists not involved in study. Drop outs: 1.2%
Participants	Adults with solid cancer treated with 5-FU. 81 enrolled 80 completed
Interventions	2 groups, placebo versus sucralfate mouthwash (10 ml mouthwash for 2 minutes then swallow 4 times per day)
Outcomes	Mucositis severity (patient daily diary scores). Other reported outcomes: pain eating/drinking difficulty, quality of life score, weight loss, nausea and vomiting
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "permuted block randomisation was used to allocate patients to the treatment with sucralfate suspension or placebo with identical appearance" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Quote: "the study nurse, in accordance with usual clinical practice estimated the severity of mucositis retrospectively. This person was blinded to treatment allocation" Comment: no information given about other support staff.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "Investigators, treating physicians, and study subjects were all blinded to study allocation" Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Quote: "Investigators, treating physicians, and study subjects were all blinded to study allocation" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	81 patients randomised. 1 patient was excluded from the placebo group 1/40. Remaining randomised patients included in outcome assessment. 89 missing data days (14%) in sucralfate group and 63 (11%)

		in placebo. Method of assigning values for missing data to give conservative outcome estimate clearly described
Selective reporting (reporting bias)	Unclear risk	81 patients randomised. 1 patient was excluded from the placebo group 1/40. Remaining randomised patients included in outcome assessment. 89 missing data days (14%) in sucralfate group and 63 (11%) in placebo. Method of assigning values for missing data to give conservative outcome estimate clearly described
Other bias	Unclear risk	Authors suggest underreporting of mucositis by study staff due to the retrospective method of assessment

Oberbaum 2001

Methods	Randomised, parallel group study conducted in Israel. Clear information about withdrawals: 1/16 control, 1/16 test. Unclear if dentist involved in study. Drop outs: 6%. Duration: unclear
Participants	Children and adults with mixed cancer receiving a BMT. 32 consecutive patients enrolled, 30 completed
Interventions	2 groups, placebo versus traumeel (homeopathic) rinse vigorously 30 sec before swallowing 5/day for a minimum 14 days
Outcomes	Mucositis WHO scale evaluated every 2 days. Assessment used: day 7. Other reported outcomes: subjective symptom score for dry mouth, oral pain and difficulty in eating
Notes	All patients twice daily chlorhexidine, oral amphotericin B, gentle toothbrushing. Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomisation code was prepared by the manufacturer (HEEL) and was revealed only on completion of the study." Comment: random component not described.
Allocation concealment (selection bias)	Low risk	Quote: "packages of Traumeel S and placebo were prepared by the HEEL com-

Oberbaum 2001 (*Continued*)

		pany and were identified by serial number only" Comment: adequate.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "all evaluations were performed blind by the same observer (the study nurse)" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	32 patients randomised. 2 patients (1/15 placebo and 1/15 traumeel S), received a single dose of study drug and then refused further treatment. Patients not included in analysis.
Selective reporting (reporting bias)	Unclear risk	Data presented for individual AUC scores (table 3), and mean AUC scores for each group
Other bias	Low risk	No other sources of bias identified.

Okuno 1999

Methods	Randomised, parallel group study conducted in USA. Clear information about withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: up to 5 weeks after initial chemotherapy. Dentist involvement unclear
Participants	Adults with cancer (type unclear) receiving chemotherapy with 5-FU, 134 eligible, enrolled and 134 evaluated by physician, but patient assessment only completed by 124 patients
Interventions	2 groups, placebo versus glutamine (4 g twice a day, swish for 10 seconds, then swallow)
Outcomes	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
Notes	All patients used ice chips 5 minutes before 5-FU for 30 minutes. Funding source: government.
Risk of bias	

Okuno 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were subsequently randomised to receive 4 g of glutamine or an identical appearing placebo twice daily for 14 days" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	134 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Physician judged mucositis scales presented for 134 patients by grade (table 3). Patient judged scores presented for 124 patients (table 4)
Other bias	High risk	Statistically significant age difference between placebo and intervention group (P = 0.01)

Panahi 2009

Methods	Randomised, parallel group study conducted in Iran. Clear information on withdrawals. Unclear if dentist involved in study. Duration: 3 days
Participants	Adults with solid tumours (colon, breast, stomach, pancreas, rectum, esophagus and other) receiving chemotherapy
Interventions	2 groups, placebo versus allopurinol (1 mg/ml), patients asked to swish 20 ml of mouthwash for 30 seconds at 1 hr, 2 hrs and 3 hrs after chemotherapy

Outcomes	Mucositis assessed 3 times (day 1, day 3 and day 7) using the WHO scale. Other reported outcome measures: use of dentures and education (multiple logistic regression)
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were divided randomly into two groups and received allopurinol mouthwash (1 mg/ml) or placebo in a double blind fashion" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Quote: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Quote: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	33 patients recruited. 3 patients excluded due to inappropriate use of the mouthwash. Authors do not state which arm excluded patients were randomised to
Selective reporting (reporting bias)	Low risk	Data presented in the text (and in figure 1) for the distribution of mucositis grades by arm
Other bias	Low risk	Study appears to be free of other sources of bias.

Peterson 2009

Methods	Parallel group study. Duration 14 days treatment from the beginning of cycle 2 of chemotherapy, final follow-up at day 21+/-2. Dentist involvement - unclear
Participants	Inclusion criteria: aged > 18 years with colorectal cancer, undergoing chemotherapy & having experienced grade 2 or greater OM in cycle 1. Patients had to have WHO grade 0 OM at study entry and ECOG performance status </= 2 Exclusion: pregnancy, lactation, administration of other investigational drugs within 14 days of start of study or plans to use topical or systemic treatments for OM during study, radiotherapy to head & neck, alcohol or drug abuse, active fungal or herpetic infection Number randomised 99; number completed 98.
Interventions	3 groups: low dose (n = 33) 10 mg/ml recombinant human intestinal trefoil factor (rhITF) in aqueous solution dispensed as 3.5 ml spray vial. Patients (all outpatients) administered 3 puffs (approx 100 ul each) to oral mucosa 8 times daily for 14 days. High dose (n = 33) 80 mg/ml rhITF, administered as above. Placebo (n = 33) water packaged and administered as above
Outcomes	Incidence of grade 2 or greater OM, duration of grade 2 or greater OM
Notes	Funding source: the GI company (private pharma). All patients received analgesia as required but dose was low and comparable between groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "eligible patients who had developed WHO grade > 2 OM in the first cycle of chemotherapy were randomised in a 1:1:1 ratio to receive one of two doses of rhITF or a matched placebo oral spray during the second cycle of chemotherapy" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Low risk	Quote: "The placebo oral sprays were manufactured by the GI company." Intervention was manufactured in the US and conducted in Russia. Therefore, carers likely to be blinded
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.

Peterson 2009 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	99 patients randomised. 1 patient (1/33 low dose rhITF) lost to follow-up on day 21. Patient included in overall incidence of OM incidence data
Selective reporting (reporting bias)	Low risk	Data presented for all patients by grade and treatment arm (fig 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Pfeiffer 1990

Methods	Randomised, cross-over study conducted in Denmark. Unclear information about withdrawals. Dentist not involved in study. Drop outs: 43%. Duration: 14 days
Participants	Adults with head and neck cancer. 40 patients enrolled, 23 evaluable
Interventions	2 groups, placebo versus sulcralfate (1 g 15 ml suspension, swish for 2 min then spit out or swallow)
Outcomes	Ulceration or not. Assessment used: day 14. Other reported outcomes: pain, problems eating
Notes	Funding source: pharmaceutical support for product.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to receive either sucralfate-placebo or placebo-sucralfate" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Pfeiffer 1990 (*Continued*)

Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind. Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	High risk	40 patients randomised. Only 23 patients (58%) included in the outcome assessment. 5 due to change to chemotherapy regimen, 2 died, 10 not evaluable due to 'swishing' (7 had increased nausea and 3 excluded due to poor compliance). Authors give no information about which arms excluded patients were allocated
Selective reporting (reporting bias)	Unclear risk	Data presented for numbers of patients in each treatment arm experiencing erythema, edema, erosion and ulceration (table 2)
Other bias	High risk	Mode of application changed after 18 patients (next 22 patients were asked to swish and expectorate the solution rather than swallowing)

Pillsbury 1986

Methods	Randomised, parallel study conducted in USA. Clear information about withdrawals, 2/10 control, 0/10 test. Dentist involved in study. Drop outs: 10%. Duration: until treatment was completed.
Participants	Adults with head and neck cancer. 20 enrolled, 18 completed.
Interventions	2 groups, placebo versus prostaglandin inhibitor (25 mg of indomethacin 4 times per day)
Outcomes	Mucositis grade at day 1, 2 and 3.
Notes	Funding source: none.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Ten patients received indomethacin, 25 mg four times

Pillsbury 1986 (*Continued*)

		a day, whereas the others received placebo during the entire course of treatment in a double-blind fashion" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 patients recruited. 1 patient withdrew from control group. Authors give complete reasons for withdrawal. In addition, 1 patient in control group was excluded because they had not yet completed treatment. Mucositis data presented for 18 patients.
Selective reporting (reporting bias)	Unclear risk	Data presented for mucositis grade at days 1-3 for 18 patients (table 1).
Other bias	Low risk	Study appears to be free of other sources of bias.

Pitten 2003

Methods	Randomised, parallel group study conducted in Germany. Clear information about withdrawals: none. Dentist involved in study. Drop outs: 0%
Participants	Adults with mixed cancer treated with chemotherapy, 47 enrolled, 47 completed
Interventions	2 groups, placebo versus chlorhexidine 100 ml 0.3% chlorhexidine, 10.4 g ethanol, 1.67 g hydrogen peroxide versus stannous fluoride
Outcomes	Mucositis WHO grading. Other reported outcomes: systemic infection, febrile episodes, blood changes, microbial counts
Notes	Funding source: external.

Pitten 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the patients were assigned to one of the two treatment groups by stratified block randomisation; the blocks were selected using a set of random sampling numbers" Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "the rinses were filled into brown glass bottles by the pharmacy of the University of Greifswald, which was responsible for randomisation"
Blinding (performance bias and detection bias) Carers	Low risk	Quote: "Neither the patient, nor the dentist knew whether the patient received the chlorhexidine based product or the control medication. In addition, none of the nurses, physicians, or oncologists knew the specific drug used for oral rinsing"
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "Neither the patient, nor the dentist knew whether the patient received the chlorhexidine based product or the control medication. In addition, none of the nurses, physicians, or oncologists knew the specific drug used for oral rinsing"
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "Neither the patient, nor the dentist knew whether the patient received the chlorhexidine based product or the control medication. In addition, none of the nurses, physicians, or oncologists knew the specific drug used for oral rinsing"
Incomplete outcome data (attrition bias) All outcomes	Low risk	47 patients randomised. No incomplete outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for 47 patients by mucositis grades 0-1 and 2-4 (table 4)
Other bias	High risk	Data from unplanned interim analysis.

Prada 1987

Methods	Randomised, parallel group study conducted in Italy. Unclear information about withdrawals. Dentist not involved in study. Drop outs: 10%. Duration: 10 days
Participants	Adults with head and neck cancer. 40 patients eligible and enrolled, 36 evaluated
Interventions	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)
Outcomes	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
Notes	Funding source: none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:."...according to the randomization code". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "8 anonymous and indistinguishable bottles... " Comment: unclear if bottles were sequentially numbered.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	40 patients randomised. 4 patients withdrew (1/20 benzydamine, 3/20 control). Authors give no reasons for withdrawal
Selective reporting (reporting bias)	Unclear risk	Data presented for onset of mucositis (probability analysis) (fig 1) and the number of patients with mucositis in each arm (text).

Prada 1987 (*Continued*)

Other bias	High risk	Not all patients had an oral mucositis score of 0 when entering the study. Double blind study. However, placebo patients also received paracetamol for pain control

Puataweepong 2009

Methods	Parallel group study. Duration 8 weeks (throughout 3-4 weeks of radiotherapy and until 8 week follow-up. Dentist involvement - unclear
Participants	Inclusion criteria: stage 2-4 histologically confirmed head and neck cancer planning to undergo adjuvant or definitive radiotherapy. Karnofsky performance status > 70% Exclusions: prior RT, history of allergy to aloe vera, underlying diabetes mellitus, HIV positive Number randomised 61; completed 60; evaluated 61.
Interventions	2 groups: A (n = 30) 15 ml aloe vera solution 3 times daily beginning on day 1 of RT. B (n = 31) 15 ml of placebo (identical in taste and appearance) 3 times daily beginning on day 1 of RT
Outcomes	Onset & incidence of severe mucositis, weight loss, number of patients & duration of radiotherapy interruption, adverse events, requirement for analgesics, antibiotics, antifungals
Notes	Funding source: The Thailand Research Fund. All patients received daily supportive care including rinsing mouth with water, saline or viscous lidocaine. Analgesic drugs and antibiotics were allowed and feeding tubes were used as required

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "double blind randomised placebo controlled trial". Quote: "Stratified block randomisation". Comment: insufficient information to determine 'yes' or 'no'
Allocation concealment (selection bias)	Unclear risk	Quote: "The allocation was concealed". Comment: insufficient information to determine 'yes' or 'no'
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Puataweepong 2009 (*Continued*)

Blinding (performance bias and detection bias) Patients	Low risk	Quote: "The allocation was concealed and blinded to physician, patients and personnel involved in the study" Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "The allocation was concealed and blinded to physician, patients and personnel involved in the study" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	61 patients recruited. 1 patient (1/31 placebo group) discontinued but was included in mucositis data
Selective reporting (reporting bias)	Low risk	Data presented in percentages for mucositis incidence by grade and arm. Data also presented for the incidence of severe mucositis by arm
Other bias	High risk	Significant baseline imbalances between the study arms: gender (P = 0.03), previous smoking (P = 0.056), previous surgery (P = 0.04)

Qin 2007

Methods	Randomised, parallel group study conducted in China. Withdrawals: 0. Unclear if dentist involved in study, duration: duration of therapy
Participants	Adults and children aged 16 to 70 with nasogastric carcinoma receiving radiotherapy (total dose 50-78 Gy)
Interventions	2 groups, no treatment control versus dental stent (worn by patients during radiotherapy)
Outcomes	Mucositis assessed using a 0-4 scale. Other reported outcome measures: weight loss, taste disruption
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: random component not described.

Qin 2007 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Incomplete outcome data (attrition bias) All outcomes	Low risk	43 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Data presented for all patients by grade of mucositis and arm
Other bias	High risk	ROB assessed from translation. Baseline imbalance: control group experienced more taste dysfunction at baseline

Rahn 1997

Methods	Randomised, parallel group study conducted in Germany. Clear information about withdrawals: none. Dentist involvement unclear. Drop outs: 0%. Duration: until 1 week after end of radiotherapy
Participants	Adults with head and neck cancer. 40 patients eligible, enrolled. 2 died but all 40 were evaluated
Interventions	2 groups, control (sterile water) versus povidone iodine rinse (rinsing for 3 mins with 100 ml solution 4 times daily)
Outcomes	WHO assessment of mucositis on 0-4 scale. During therapy and at 2, 6 weeks after therapy. Assessment used: day 28
Notes	All patients received nystatin, dexpanthenol, ratoside and immunoglobin. Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Rahn 1997 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "40 patients were enrolled in the study and randomly assigned to a treatment or control group" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Quote: "Open, placebo controlled and randomised clinical trial"
Blinding (performance bias and detection bias) Patients	High risk	Quote: "Open, placebo controlled and randomised clinical trial"
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "Open, placebo controlled and randomised clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients recruited. 37 patients completed the study. Authors give incomplete reasons for attrition/exclusion. Mucositis data presented for 40 patients
Selective reporting (reporting bias)	Low risk	Data presented for grades of mucositis for 40 patients (figure 3)
Other bias	Low risk	Study appears to be free of other sources of bias.

Rashad 2008

Methods	Randomised parallel group trial conducted in Egypt. Duration of follow-up 7 week.s
Participants	Adults with histologically confirmed SCCHN T1-4, N0-3, m0, KPS $\geq$ 50%. 40 randomised and evaluated. Recruited April 2005 to July 2006
Interventions	Honey (from Trifolium Alexandrenum) versus no treatment. 15 min before, 15 min after and 6 hours after radiotherapy patients smeared mouth with honey, and then swallowed slowly to smear honey on mucosa
Outcomes	WHO mucositis grade, weekly during therapy (7 weeks) 4-week data used
Notes	All patients received chemoradiotherapy (60-66 Gy plus cisplatin 20 mg/m^2 weekly) for 6-7 weeks.

Rashad 2008 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "enrolled patients were randomised to either the treatment group, to receive concomitant chemotherapy and radiotherapy plus topical application of pure natural honey, or the control group, to receive concomitant chemotherapy and radiotherapy without honey" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Honey versus no intervention. Blinding impossible.
Blinding (performance bias and detection bias) Patients	High risk	Honey versus no intervention. Blinding impossible.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Honey versus no intervention. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Data presented for grade of mucositis by arm for 40 patients
Other bias	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Rocke 1993

Methods	Randomised parallel group study conducted in USA. Clear explanation of withdrawals: 1 in 30 min arm. Drop outs: < 1%. Duration: 5 days
Participants	Adults receiving first course of 5-FU, cancer type unclear. 179 eligible, and randomised, 178 evaluated
Interventions	2 groups, 30 versus 60 minute cryotherapy. Ice chips placed in mouth 5 min before 5-FU and then swished round during treatment and replenished as ice melted

Rocke 1993 (*Continued*)

Outcomes	Physician and patient assessment of mucositis on 0-4 scale.
Notes	Some cross-over data were included in paper. We have not included this as only patients with mild mucositis crossed-over

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to receive cryotherapy for either 30 or 60 minutes" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	30 minutes versus 60 minutes of cryotherapy. Blinding impossible
Blinding (performance bias and detection bias) Patients	High risk	30 minutes versus 60 minutes of cryotherapy. Blinding impossible
Blinding (performance bias and detection bias) Outcome assessors	High risk	30 minutes versus 60 minutes of cryotherapy. No apparent blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	179 patients recruited. 1 patient withdrawn. 1/90 30-minute cryotherapy. Authors give reason for attrition
Selective reporting (reporting bias)	Low risk	Physician judged mucositis scores presented for 178 patients (table 2). Patient judged scores presented for 163 patients (table 3)
Other bias	Low risk	Study appears to be free of other sources of bias.

Rosen 2006

Methods	Randomised, parallel group multisite study conducted in the USA and Australia. Clear information on withdrawals. Unclear if dentist involved in study
Participants	Adults with tumours of the colon and rectum receiving chemotherapy or chemoradiotherapy. All patients received leucovorin 20 mg/m^2/day and fluorouracil 425 mg/m^2/day for 5 consecutive days.
Interventions	2 groups, placebo versus palifermin (40 μg/kg) for 3 days before chemotherapy administration
Outcomes	Mucositis assessed on days 1, 4, 8, 12, and 15 and day 28 using the WHO score. Patients completed the oral mucositis daily questionnaire daily between days 1 and 27. Other reported outcomes: diarrhoea, patient reported mouth and throat soreness, safety, laboratory assessments, disease outcomes, antibody assessments
Notes	Funding source: pharmaceutical (Amgen).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned (by centre and prior chemotherapy) in a 1:1 ratio to receive palifermin or placebo" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	65 patients recruited. 64 patients received study drugs. No patients discontinued during 1st cycle (data used in meta-analysis). 10 patients withdrew during 2nd cycle of chemotherapy. 8/28 palifermin and 2/36 placebo.

Rosen 2006 (*Continued*)

Selective reporting (reporting bias)	Low risk	Data presented in percentages for all patients by mucositis grade (figure 2a)
Other bias	Low risk	Study appears to be free of other sources of bias.

Saarilahti 2002

Methods	Randomised, parallel group study conducted in Finland. Clear information about withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration: 10 weeks
Participants	Adults with head and neck cancer. 40 patients eligible, enrolled between October 1999 and April 2001, and evaluated.
Interventions	2 groups, GM-CSF mouthwash made by dissolving 150 mg of dried powder in 100 ml sterile water versus mouthwash of 4 g sucralfate with 100 ml sterile water. 4 doses x 25 ml per day after meals
Outcomes	RTOG rating for mucositis on 0-4 scale. Author provided data in right form for the review
Notes	Maximum value of mucositis taken.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done using computer generated digits"
Allocation concealment (selection bias)	Low risk	Quote: "After patients provided written consent, they were assigned to a treatment group by way of a telephone call to the randomisation office" Quote: "The drug vials were marked with a study code that prevented identification of the allocation group" Comment: central method of randomisation.
Blinding (performance bias and detection bias) Carers	Low risk	Comment: double blind study with adequate allocation concealment, drugs prepared by pharmacy
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.

Saarilahti 2002 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for mean mucositis score over time (fig 1) and mean mucosal pain scores (fig 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Scarantino 2006

Methods	Randomised, parallel group study conducted in USA. Clear information on withdrawals: 1 in pilocarpine and 2 in placebo group refused protocol treatment. Dentist not involved in study. Drop outs: 1%. Duration: 13 weeks
Participants	Adults with head and neck cancer. Planned radiotherapy to include have 50% of the volume of the major salivary glands receive 50 Gy. 249 enrolled, 4 ineligible, 245 randomised, 242 completed
Interventions	2 groups, placebo versus pilocarpine 5 mg 4 times per day.
Outcomes	Mucositis graded 3 times per week according to the RTOG acute mucositis toxicity scale (0-4). Assessment used: unclear. We used the highest RTOG score recoded. Other reported outcomes: sialometry of unstimulated and stimulated whole saliva, eating, taste swallowing, pain, adverse events included nausea and vomiting
Notes	Funding source: government. Pharmacological company provided drug and organised randomisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "249 patients were randomised: 124 to receive 5 mg of pilocarpine four times daily and 125 to receive a placebo on the same schedule" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Scarantino 2006 (*Continued*)

Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	249 patients randomised. 4 patients were later deemed ineligible. A further 3 patients withdrew (1/121 pilocarpine, 2/124 placebo). Authors give full reasons for exclusions/withdrawals
Selective reporting (reporting bias)	Unclear risk	Data presented for 242 patients by grade of mucositis for grades 0, 1 and 2+
Other bias	Unclear risk	Baseline imbalance: more patients with a KPS of 90-100 were in the pilocarpine group (P+0.03). However, it is unclear how this would affect mucositis development

Scherlacher 1990

Methods	Randomised, parallel group study conducted in Germany. Clear description of withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration 6-7 weeks
Participants	Adults with head and neck cancer. 45 eligible.
Interventions	2 groups: usual care control versus sucralfate suspension (1 g orally 4 times per day for 5 mins)
Outcomes	Mucositis scored on 1-5 scale and number with mucositis 3-5 given
Notes	Both groups received standard oral hygiene, frequent tooth cleaning and disinfection of oral and pharyngeal mucosa. Funding source: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement

Scherlacher 1990 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "random allocation to test and control group". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	45 patients recruited. Outcomes given in percentages.
Selective reporting (reporting bias)	Unclear risk	Data presented for number of patients with mucositis grades 3-5
Other bias	High risk	Risk of bias assessed from translation.

Schneider 1999

Methods	Randomised, parallel group study conducted in USA. Clear information about withdrawals: none. Dentist involved in study. Drop outs: 0%
Participants	Adults with head and neck cancer. 14 patients enrolled and evaluated. Recruitment January 1995 to April 1996
Interventions	2 groups, placebo versus filgrastim (subcutaneous injections daily throughout treatment titrated to keep neutrophil count between 10x 10^9/l and 30x 10^9/l).
Outcomes	WHO mucositis 0-4 scale, and Hickey mucositis scores. Proportion of patients greater than WHO mucositis grade 3 presented. Assessment used: week 10
Notes	All patients had oral hygiene instruction. Funding source: pharmaceutical

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomised equally between the two treatment groups to receive either subcutaneous injections of filgrastim or placebo starting concurrently with the first day of radiation and continuing daily" Comment: random component not described.
Allocation concealment (selection bias)	Low risk	Quote: "Amgen Inc. prepared and packaged all drug and placebo in identical containers, with the only designator being the randomisation number. The study material and randomisation list were held by the UCLA pharmacy for the duration of the study" Comment: pharmacy controlled randomisation.
Blinding (performance bias and detection bias) Carers	Low risk	Pharmacy controlled randomisation. Unlikely that carers would know allocations
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double Blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double Blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 patients randomised. 1 patient withdrew, however, results were included in analysis. No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Data presented for mean worst Hickey mucositis score by week (fig 1) and mean worst WHO mucositis by week (fig 2) and the proportion of patients whose scores remained below 3 by week (fig 3 and fig 4)
Other bias	High risk	Study was stopped after an interim analysis. Authors state that "owing to administrative obstacles completion of the trial is not possible". Authors do not meet either of their previously stated early stopping rules

Schubert 2007

Methods	Randomised, parallel group study conducted in the USA. Clear information about withdrawals. Duration: 7-13 days
Participants	Adults (children over 12 could be recruited, however, youngest participant appears to have been 18) undergoing transplantation (both allogeneic and autologous). Conditioning: busulfan and cytoxan, TBI and cytoxan, fludarabine and busulfan, and other
Interventions	3 groups, sham laser versus laser (650 nm, (40 mW)) laser, versus laser (780 nm (60 mW)). Laser therapy started on the first day of conditioning and continued for 3 days post-transplant
Outcomes	Mucositis assessed using the oral mucositis index on days 0, 4, 7, 11, 14, 18, and 21. Other reported outcomes: oral pain, adverse events (death)
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "subjects who consented were randomised into one of two laser treatment arms or a placebo therapy group" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Quote: "by having subjects wear both laser safety goggles and a soft cloth blindfold, it was physically impossible for them to see the tip of the laser emitting device or the control panel of the unit, thus ensuring that subjects were blinded as to whether they were receiving actual laser" Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Quote: "mucositis examinations were carried out by trained and calibrated oral medicine personnel who were blind to the subjects treatment arm assignment" Comment: probably done.

Schubert 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	70 patients randomised. 2 patients died during study. 67% had scores for all time points and a similar number in each group had missing data. Self assessment of pain was only completed by 17/70 patients
Selective reporting (reporting bias)	Unclear risk	Data presented for mean mucositis scores over time (fig 1) and mean mucositis scores by arm (table 2)
Other bias	High risk	Patients in the 650 nm laser arm were significantly more likely to have received a conditioning regimen which included TBI

Shenep 1988

Methods	Randomised, parallel group study conducted in USA. Clear information about withdrawals: none. Dentist not involved in study. Drop outs: 0%. Duration: 50 days
Participants	Children with leukaemia. Chemotherapy- remission induction multiagent ANLL-83. 48 patients enrolled and evaluated
Interventions	2 groups, placebo versus sucralfate (0.75 mg/kg daily, suspension swished every 6 hours)
Outcomes	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
Notes	Clinician's mucositis score used. Funding source: government.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomisation of treatment for patients was performed by the hospital pharmacist according to a scheme obtained from Biostatics Division." Comment: random component not described.
Allocation concealment (selection bias)	Low risk	Pharmacy controlled randomisation.
Blinding (performance bias and detection bias) Carers	Low risk	Double blind study with adequate allocation concealment.

Shenep 1988 (*Continued*)

Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	48 patients recruited. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for observed mucositis and patient reports of mucositis at grades 0, 1 and > 2 (table 3)
Other bias	Low risk	Study appears to be free of other sources of bias.

Shieh 1997

Methods	Randomised, parallel group study conducted in China. Clear information about withdrawals: none. Dentist involved in study. Drop outs: 0%. Duration: 5 weeks
Participants	Adults with head and neck cancer. 30 patients were enrolled between June 1994 and May 1995 and all evaluated
Interventions	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. Data from E1 and E2 combined as oral care intervention
Outcomes	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
Notes	Funding source: government.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "to achieve an equal number of study subjects in each group, every 3 consecutive entries of eligible patients over time were treated as a block wherein a simple randomisation was performed" Comment: random component not described. However, reference made to ran-

Shieh 1997 (*Continued*)

		domisation article
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	2 different methods of oral care (E1/ E2) versus control. Blinding impossible
Blinding (performance bias and detection bias) Patients	High risk	2 different methods of oral care (E1/ E2) versus control. Blinding impossible
Blinding (performance bias and detection bias) Outcome assessors	High risk	2 different methods of oral care (E1/ E2) versus control. No apparent blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	30 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented in the text for the percentage of patients with mucositis at week 2. Data also presented for onset time of stomatitis (figure 1), percentage incidence of stomatitis by treatment day (figure 2) , mean OAG scores compared to days of treatment (figure 3), and increases in mean OAG score by treatment day (figure 4)
Other bias	High risk	Baseline OAG score was 1.5 point higher for the E1 group due to random allocation of 3 patients with history of betel nut chewing to this group. Authors state that conclusions regarding the mean onset of mucositis did not change after these patients were excluded from the analysis. However, mean OAG scores are not provided for comparison.

Sorensen 2008

Methods	Randomised, parallel group study conducted in Denmark. Clear information about withdrawals. Unclear if dentis involved in study. Drop outs: 8%
Participants	Adults with gastric or colorectal cancer treated with 5-FU containing chemotherapy, 225 enrolled, 206 completed
Interventions	3 groups, placebo (saline mouthrinse 3 times/day) versus chlorhexidine mouthrinse (3 times/day) versus crushed ice

Outcomes	CTC v2 grading of mucositis. Assessment used: day 28. Other reported outcomes: patient reporting of severity and duration of mucositis, compliance	
Notes	Funding source: government.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised after informed consent to 1 of 3 prophylactic regimens" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "identical 500 mL bottles labelled x and y". Comment: unclear if bottles were sequentially numbered.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	150 patients randomised to double blind arms. 11 patients withdrew (2/75 chlorhexidine, 9/75 placebo). 139 patients included in final analysis 75 patients randomised to cryotherapy arm. 8 patients did not return questionnaire on side effects and compliance and were removed from final analysis. 67 patients included in final analysis
Selective reporting (reporting bias)	Low risk	Data presented for mucositis by grade and treatment arm.
Other bias	Low risk	Study appears to be free of other sources of bias.

Sornsuvit 2008

Methods	Randomised, parallel group study conducted in Thailand. No withdrawals, losses to follow-up described. Unclear if dentist involved in study. Duration: 5 days concurrently with each chemotherapy cycle. Recruitment period: not stated
Participants	Adults with acute myeloid leukaemia. 16 patients eligible, and evaluated
Interventions	2 groups, glutamine 30 g/day IV or and equivalent quantity of standard amino acid mixture (control) each day on days 1-5 of each chemotherapy cycle
Outcomes	Grades for mucositis on 0-4 scale, blood changes, infection, weight loss, adverse effects
Notes	Any mucositis, ≥ grade 2 mucositis, ≥ grade 3 mucositis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised to receive intravenous supplementation with either 30 g/day Gln or an equivalent quantity of a standard amino acid mixture" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Unclear risk	Glutamine versus standard amino acids.
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Glutamine versus standard amino acids.
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for mean severity grade, number of patients with mucositis > 2 and number of patients with mucositis > 3 (table 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Spencer 2005

Methods	Randomised, parallel group, multicentre study conducted in Australia. Clear information on withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration: up to 46 months
Participants	Adults blood cancer - multiple myeloma undergoing BMT high dose melphalan conditioned autologous stem cell transplantation (ASCT). Between May 1999 and November 2000, 90 patients were randomised, with 82 evaluable at end of trial
Interventions	2 groups, no treatment control versus amifostine (patients undergoing ASCT were randomised to receive or not receive amifostine 910 mg/m² prior to melphalan 200 mg/m²)
Outcomes	Mucositis graded according to the adapted WHO toxicity scale. Assessment used: time unclear. Other reported outcomes: parenteral nutrition, analgesic use, complete remission, adverse events included: toxicity, nausea (grade 1), vomiting and hypotention
Notes	Funding source: industry and charity. All participants received antibacterial prophylaxis and fluconazole. Pharmacological company provided drug and organised randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomised to receive Mel200 with or without amifostine 910 mg/m2 pretreatment 15-30 mins prior to melphalan infusion." Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Quote: "open label".
Blinding (performance bias and detection bias) Patients	High risk	Quote: "open label".
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "open label".
Incomplete outcome data (attrition bias) All outcomes	Low risk	90 patients randomised. 82 patients were evaluable at the end of the trial. Authors do not denote which group withdrawals were from. ITT analysis performed

Spencer 2005 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Data presented for percentage of patients with grade 0, grades 1/2 and 3/4 mucositis (figure 1), median mucositis grade, median duration (table 5) and percentage of patients with no mucositis
Other bias	Low risk	Study appears to be free of other sources of bias.

Spielberger 2004

Methods	Randomised, parallel group, multicentre study conducted in USA. Clear information on withdrawals: none. Dentist involved in study. Drop outs: 0%. Duration: 28 days
Participants	Adults with mixed cancer. BMT. Treated with fractionated total-body irradiation plus high-dose chemotherapy and auto-HSCT. 212 enrolled, randomised and completed
Interventions	2 groups, placebo versus palifermin (recombinant human keratinocyte growth factor) 60 micrograms per kilogram of body weight per day iv for 3 consecutive days immediately before the initiation of conditioning therapy
Outcomes	Mucositis assessed daily using 3 scales: the WHO oral-toxicity scale (0-4) (primary scale) , RTOG (0-4) acute radiation morbidity scoring criteria for mucous membranes, and the 4-grade Western Consortium for Cancer Nursing Research (WCCNR) revised staging system for oral mucositis. Assessment used: -8 up to day 28. Other reported outcomes: soreness of the mouth and throat, swallowing limitations, opioid use, incidence of febrile neutropenia, incidence of infections, incidence of the use of total parenteral nutrition. Adverse events: included rash, purities, erythema, taste alteration
Notes	Funding source: industry. Pharmacological company provided drug and organised randomisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised in a 1:1 (stratified according to centre and type of hematologic cancer) to receive Palifermin or placebo" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Spielberger 2004 (*Continued*)

Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	214 patients randomised. 212 patients received at least 1 dose of palifermin. 7 patients did not complete the study: 2/106 palifermin, 4/106 placebo. Authors give no reasons for non-completion. Mucositis data given for 212 patients
Selective reporting (reporting bias)	Low risk	Data presented in percentages for 212 patients by mucositis grade (figure 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Spijkervet 1989

Methods	Randomised, parallel group study conducted in The Netherlands. Clear information about withdrawals: none. Dentist involved in study. Drop outs: 0%. Duration: 5 weeks
Participants	Adults with head and neck cancer treated with radiotherapy. 30 patients eligible, enrolled and evaluated
Interventions	2 groups, placebo versus chlorhexidine spray/rinse (0.1% chlorhexidine 100 ml per day (spray 50 ml) rinsing 3 times with 15 ml)
Outcomes	Semiquantitative scoring of mucositis in "described elsewhere". Assessed thrice weekly until end of treatment (at least 50 Gy). Assessment used: day 35. Other reported outcomes: microflora
Notes	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.

Risk of bias

Bias	Authors' judgement	Support for judgement

Spijkervet 1989 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "This study was a prospective, double-blind, randomised placebo controlled program." Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	30 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for number of patients with severe mucositis (pseudomembrane formation) in text.
Other bias	Low risk	Study appears to be free of other sources of bias.

Stokman 2003

Methods	Randomised, parallel group study conducted in The Netherlands. Clear information on withdrawals: 2/32 placebo, 5/33 test. Unclear whether dentist involved in study. Drop outs: 10.7%
Participants	Adults with head and neck cancer. 65 enrolled, 58 completed.
Interventions	2 groups, placebo versus active lozenges (containing polymyxin E 2 mg, tobramycin 1. 8 mg and amphotericin B 10 mg (PTA))
Outcomes	Percentage developing mucositis (WHO 3-4). Other reported outcomes: weight loss
Notes	Funding source: unclear.
Risk of bias	

Stokman 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed by the hospital pharmacist according to a computer-generated, randomised allocation schedule" Comment: computer generated randomisation.
Allocation concealment (selection bias)	Low risk	Pharmacy controlled randomisation.
Blinding (performance bias and detection bias) Carers	Low risk	Adequate allocation concealment. Unlikely that carers would know of allocations
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "Patients, clinicians, dental hygienists and microbiologists were blind for who was taking antibiotics"
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "Patients, clinicians, dental hygienists and microbiologists were blind for who was taking antibiotics"
Incomplete outcome data (attrition bias) All outcomes	Low risk	65 patients randomised. 7 patients withdrew (5/33 PTA, 2/32 placebo). ITT analysis performed
Selective reporting (reporting bias)	Unclear risk	Data presented for mean mucositis score by weeks of radiation in a graph (fig 1) and a table (table 2). Percentages of patients with grades 3 and 4 mucositis presented in the text
Other bias	Low risk	Study appears to be free of other sources of bias.

Su 2004

Methods	Randomised, parallel group study conducted in USA. Clear information about withdrawals: 0. Unclear if dentist involved in study. Drop outs: 0%
Participants	Adults with head and neck cancer. 58 enrolled, 58 completed.
Interventions	2 groups, placebo versus aloe vera solution (AV). 20 cc aloe vera a day during radiotherapy
Outcomes	Mucositis RTOG grade 3-4. Other reported outcomes: mean overall health, mean soreness score

Notes	Funding source: none.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the assignment procedure was termed "biased coin" randomization and ensures that the number of subjects assigned to aloe vera would be roughly equal to those receiving chemotherapy and those with the same primary care site." Comment: biased coin randomisation.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Quote: "To minimize biases, both study physicians and patients were unaware of the results of randomisation" Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Quote: "To minimize biases, both study physicians and patients were unaware of the results of randomisation" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	58 patients recruited. All patients included in analysis. Mucositis data (table 2) presented in percentages
Selective reporting (reporting bias)	Unclear risk	Data presented for grade 2-3 mucositis in percentages (table 2) and maximum toxicity grade (table 3)
Other bias	Low risk	Study appears to be free of other sources of bias.

Su 2006

Methods	Randomised double blind placebo controlled parallel group study conducted in USA. Dentist involvement unclear
Participants	Adults with stage 2-4 M0 SCCHN recruited January 92 to December 96. 19 in G-CSF and 22 in placebo, all but 1 patient in placebo group completed treatment and were evaluable
Interventions	G-CSF 3 μg/kg daily SC, 7 times/week. Placebo equal volume 5% dextrose in water. Treatment started 3 days prior to radiotherapy and continued throughout. Planned dose reductions if white blood cell count exceeded set limits, assessed by investigator who communicated directly with pharmacist to maintain blinding
Outcomes	Primary: incidence of percutaneous endoscopic gastrostomy placement. Also mucositis grade, level of mucositis treatment required, overall survival, progression free survival, locoregional control
Notes	Funding source: NCI grant. Median duration of follow-up 7.25 years

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised to either G-CSF or placebo by randomly permuted blocks, after stratification by primary disease site" Comment: random component not explicit. However, setting makes adequate randomisation likely
Allocation concealment (selection bias)	Low risk	Quote: "a randomization list was prepared by the Memorial Sloan-Kettering Cancer centre biostatics service and held by the pharmacy. Investigators did not have access to this list" Comment: pharmacy controlled randomisation.
Blinding (performance bias and detection bias) Carers	Low risk	Adequate allocation concealment. Unlikely that carers would know of allocation
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.

Su 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	41 patients recruited. 1 patient (1/22 placebo) withdrew. Authors do not give reason for withdrawal.
Selective reporting (reporting bias)	Low risk	Data presented for 40 patients by grade of mucositis and arm
Other bias	Low risk	Study appears to be free of other sources of bias.

Svanberg 2007

Methods	Randomised, parallel group study conducted in Sweden. Clear information about withdrawals: 0. Dentist involved in study. Duration: during chemotherapy administration. Recruitment between January 2002 and August 2004
Participants	Adults with a mix of testicular cancer and haematological malignancies undergoing myeloablative therapy prior to bone marrow or stem cell transplantation
Interventions	2 groups, no treatment versus cryotherapy.
Outcomes	Mucositis assessed daily using the OMAS instrument. Other reported outcome measures: blood counts, c-reactive protein, compliance, adverse events. Days of intravenous opioids
Notes	45 staff members assessed mucositis using the OMAS instrument. Unclear if inter-rater reliability had been conducted before starting data collection. Probably not due to the number of staff involved Funding: government.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was a randomised controlled trial with a random assignment to experimental (EXP) or control (CTR) group" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Cryotherapy versus standard treatment. Blinding impossible.

Svanberg 2007 (*Continued*)

Blinding (performance bias and detection bias) Patients	High risk	Cryotherapy versus standard treatment. Blinding impossible.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Cryotherapy versus standard treatment. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	78 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented in the text for mucositis scores on day 10 (autologous patients), day 16 (allogeneic patients), days of mucositis
Other bias	Low risk	Study appears to be free from other sources of bias.

Symonds 1996

Methods	Randomised, parallel group study conducted in Scotland. Clear information about withdrawals: 30/139 control, 24/136 test. Unclear if dentist involved in study. Drop outs: 20%. Duration: until radiation reaction settled, 8 weeks
Participants	Adults with head and neck cancer. 275 patients enrolled and 221 evaluated
Interventions	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)
Outcomes	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
Notes	Funding source: none.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to receive either a placebo or active pastilles containing polymyxin E 2 mg, tobramycin 1. 8 mg and amphotericin B 10 mg" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Symonds 1996 (*Continued*)

Blinding (performance bias and detection bias) Carers	Low risk	Quote: "The active and placebo pastilles were identical and neither the patients, clinicians, nurses nor microbiologists were aware who were taking antibiotics" Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "The active and placebo pastilles were identical and neither the patients, clinicians, nurses nor microbiologists were aware who were taking antibiotics" Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "The active and placebo pastilles were identical and neither the patients, clinicians, nurses nor microbiologists were aware who were taking antibiotics" Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	High risk	275 patients randomised. 54 patients were unevaluable (24 pastilles, 30 placebo). Authors do not give full reasons for withdrawal/drop out
Selective reporting (reporting bias)	Unclear risk	Data presented for erythema of mucosa for 220 patients (nil/slight/moderate/severe), mucositis distribution for 221 patients (none/patchy/confluent) and mucositis area (median/IQ range/range)
Other bias	Low risk	Study appears to be free of other sources of bias.

Trotti 2004

Methods	Randomised, parallel group, multicentre study conducted in USA, Canada, Germany, France and UK between July 2000 and December 2001. Clear information about withdrawals: 0. Dentist involvement unclear. Drop outs: 0%
Participants	Adults with head and neck cancer receiving chemoradiotherapy. 545 enrolled, 511 results reported
Interventions	3 groups, placebo plus SOC, iseganan (9 mg as 0.3% aqueous solution) plus SOC, SOC alone

Outcomes	Percentage mucositis NCI CTC grade 2-4. Other reported outcomes: completion of radiotherapy and chemotherapy up to 28 days after radiotherapy
Notes	Funding source: pharmaceutical. Correspondence with Dr D Peterson: clinical trials with iseganan were discontinued approximately 6 years ago. Approval of the drug for oral mucositis was not obtained in the United States

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised double blind". Quote: "patients were randomised to receive 9 mg doses of iseganan formulated as a 0.3% aqueous vehicle solution plus institute specific standard-of-care (SOC) management of oral hygiene, or placebo (vehicle solution) plus SOC, or SOC alone in a 3:2:1 distribution" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "all study drugs were packaged in identical multidose, white, opaque plastic bottles"
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Quote: "Patients, study personnel, and the sponsor were blinded as to whether an individual received iseganan or placebo" Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Quote: "Patients, study personnel, and the sponsor were blinded as to whether an individual received iseganan or placebo" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	545 patients randomised. 27 patients were potentially affected by randomisation error and were subsequently excluded from the efficacy analysis. 7 patients additionally excluded because they did not receive the study drug/baseline assessment. Authors do

Trotti 2004 (*Continued*)

		not state which arms patients were randomised to
Selective reporting (reporting bias)	Unclear risk	Data presented for mucositis grades 0/1, 2 and 3/4 in percentages, mean peak severity of OM, and average OM
Other bias	Low risk	Study appears to be free of other sources of bias.

Tu 1998

Methods	Randomised, parallel group multisite study conducted in China. Unclear if dentist involved in study. Drop outs: 0%. Duration: 4 to 6 weeks
Participants	Data presented for 159 patients with mixed cancers receiving radiotherapy
Interventions	2 groups, placebo group (intramuscular injection of lactose liquid) versus copper zinc super oxide dismutase (SOD) (40000 units by intramuscular injection). Both groups received 1 injection a day, 5 days per week
Outcomes	Oral mucositis graded as slight, moderate and severe. Other outcome measures: skin pelvic visceral and systemic adverse events
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.

Tu 1998 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	159 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for mild and moderate to severe mucositis.
Other bias	High risk	ROB assessed from translation.

Vacha 2003

Methods	Randomised, parallel group study conducted in Germany. Clear information on withdrawals. Unclear if dentist involved in study. Duration: during radiotherapy
Participants	Adults with cancers of the larynx, oropharynx and hypopharynx receiving radiotherapy (60 Gy /70 Gy) and chemotherapy (70 mg/m^2).
Interventions	2 groups, no treatment versus amifostine (250 mg). Amifostine given over short infusion (10-15 minutes)
Outcomes	Mucositis assessed weekly using the CTC criteria. Other reported outcome measures: xerostomia, skin toxicity, body weight, performance status
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Chemotherapy and radiotherapy with or without amifostine. No apparent blinding
Blinding (performance bias and detection bias) Patients	High risk	Chemotherapy and radiotherapy with or without amifostine. No apparent blinding
Blinding (performance bias and detection bias) Outcome assessors	High risk	Chemotherapy and radiotherapy with or without amifostine. No apparent blinding

Vacha 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	56 patients randomised. 6 patients excluded. Authors do not state which arm these patients were randomised to but do give full reasons for exclusion
Selective reporting (reporting bias)	Unclear risk	Data presented for mean mucositis scores by week of treatment for both arms of the study
Other bias	Low risk	Study appears to be free from other sources of bias.

Vadhan-Raj 2010

Methods	Parallel group study, but 2 very different randomisation schedules used within this study. Duration: planned to be 6 cycles of chemotherapy but results reported based on 2 "blinded cycles" only. Dentist involvement: unclear
Participants	Inclusion criteria: patients with sarcoma who were planned to undergo multicycle chemotherapy aged 15-65 years with Karnofsky performance status >/= 80% & adequate bone marrow, hepatic and renal function Exclusion criteria: patients with history of pelvic radiation or clinically significant cardiac disease or those who had undergone surgery in previous 2 weeks were excluded Number randomised 48. Number completed (6 cycles) 25.
Interventions	2 groups: (n = 32) 180 Ug/kg palifermin IV 3 days prior to the start of each cycle of chemotherapy. (n = 16) placebo single dose IV 3 days prior to chemotherapy
Outcomes	Moderate to severe, severe mucositis according to WHO grades, adverse effects
Notes	Funding source: Amgen provided the palifermin and placebo, provided a grant to partially fund the study, and the principal investigator is a member of the Amgen board

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Two distinct computer-generated randomization lists were prepared by the Dept of Biostatistics, University of Texas MD Anderson Cancer Centre, one for the 20 patients who consented to pharmacokinetic sampling and the other for the 28 patients who did not. For the pharmacokinetics cohort the treatment allocation ratio was 4:1 palifermin:placebo in 4 blocks of 5; for the other cohort the ratio was 4:3

		palifermin to placebo in 2 blocks of 14." Comment: the clinical research team would have known that 4/5 of the pharmacokinetic group were receiving active treatment Comment: random component not described.
Allocation concealment (selection bias)	Low risk	Both randomisation lists were held by the pharmacy who assigned the patient to the next sequential slot and treatment on the basis of whether or not there was consent for pharmacokinetic sampling
Blinding (performance bias and detection bias) Carers	High risk	Quote: "the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment" Comment: however paper states that "blinding might not have been maintained due to the adverse effects of palifermin (pronounced leukoedema of buccal mucosa & gingival)", and describes cycles 1& 2 as 'blinded cycles'. Pre- and post-administration biopsies in '8 consenting patients' would have also revealed who was allocated to active treatment. Those patients consenting to the pharmacokinetic study had a 4/5 chance of receiving active treatment. Comment: we consider it likely that none of the treatment cycles were truly blinded
Blinding (performance bias and detection bias) Patients	Unclear risk	Quote: "the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment" Comment: however paper states that "blinding might not have been maintained due to the adverse effects of palifermin (pronounced leukoedema of buccal mucosa & gingival)", and describes cycles 1& 2 as 'blinded cycles'. Pre- and post-administration biopsies in '8 consenting patients' would have also revealed who was allocated to active treatment. Those patients consenting to the pharmacokinetic study had a 4/5 chance of receiving active treatment. Comment: we consider it likely that none of the treatment cycles were truly blinded
Blinding (performance bias and detection bias)	High risk	Quote: "the patient and the clinical research team (who assessed outcomes) were

Vadhan-Raj 2010 (*Continued*)

Outcome assessors		blinded to the study treatment" Comment: however paper states that "blinding might not have been maintained due to the adverse effects of palifermin (pronounced leukoedema of buccal mucosa & gingival)", and describes cycles 1& 2 as 'blinded cycles'. Pre- and post-administration biopsies in '8 consenting patients' would have also revealed who was allocated to active treatment. Those patients consenting to the pharmacokinetic study had a 4/5 chance of receiving active treatment. Comment: we consider it likely that none of the treatment cycles were truly blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12/32 (38%) and 12/16 (75%) patients in the palifermin and placebo groups respectively discontinued treatment. Some reasons are given. The reported rates of disease progression, chemotoxicity & surgery are similar in each group, but the rate of switching to open label treatment is much higher in placebo group and there is some mismatch between information in figures 1 & 3. Outcomes are reported as percentages only, and for the 'blinded cycles' 1 & 2 the numbers evaluated in each group are unclear
Selective reporting (reporting bias)	Unclear risk	Reported outcomes of moderate/severe & severe mucositis. However all reported outcomes are expressed as percentages together with a statement that "all patients were evaluable for toxicity and response to palifermin" Planned outcomes also included duration of oral mucositis, patient reported outcomes, use of narcotic analgesics, weight loss & dose reductions/delays in chemotherapy. These outcomes are not reported in the paper
Other bias	Unclear risk	Use of granulocyte macrophage colony-stimulating factor is listed as not permitted, but patients received Pegfilgrastim which is a pegylated form of human granulocyte colony-stimulating factor

van der Lelie 2001

Methods	Randomised, parallel group study conducted in The Netherlands. Clear information about withdrawals: none. Dentist involved in study. Drop outs: 0%. Duration: until neutrophil recovery
Participants	Adults with mixed cancer receiving BMT or cell stem. 39 patients eligible, 36 enrolled between May 1997 and August 1999, all evaluated
Interventions	2 groups, placebo versus GM-CSF (300 ug of GM-CSF daily dose in 2% methylocellulose gel, 5 ml gel twice daily, keep in oral cavity as long as possible then swallow)
Outcomes	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 netropenia, days in hospital
Notes	All rinsed with 0.9% saline and in case of inflamation 0.12% chlorhexidine 6 times daily. Funding source: university, pharmaceutical for intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "After giving their informed consent, the patients were randomised to receive GM-CSF or placebo" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	36 patients randomised. 8 patients withdrew. 4/18 GM-CSF, 4/18 placebo. Authors give full reasons for attrition/ exclusion
Selective reporting (reporting bias)	Unclear risk	Data presented for average WHO score, OAS and pains scores by days for both intervention and placebo group. Number of

van der Lelie 2001 (*Continued*)

		patients with grade 3 and grade 4 mucositis presented in text.
Other bias	Low risk	Study appears to be free of other sources of bias.

Veerasarn 2006

Methods	Randomised, parallel group, multicentre study conducted in Thailand. Clear information on withdrawals: none. Unclear if dentist involved in study. Drop outs: 7%. Duration: up to 90 days
Participants	Adults with head and neck cancer. 67 enrolled and randomised between February 1999 and September 2001. 62 completed
Interventions	2 groups, no amifostine control versus intravenous amifostine with radiotherapy (200 mg/m² 50 ml infusion daily 30 minutes prior to radiation treatment) (radiotherapy: 66-70 Gy or postoperative 50-60 Gy both in 2 Gy fractions)
Outcomes	Mucositis graded with reference to RTOG criteria on a 0-4 scale. Assessed at 1-6 weeks during treatment, 4 week data used for mucositis $\geq$ 2. Other reported outcomes: xerostomia, dysphasia; treatment related adverse events: vomiting, nausea, allergic reaction, haematologic, hypotension, hot flushes, somnolence, sneezing, hiccup
Notes	Funding source: pharmaceutical company.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...were randomised to receive radiotherapy or radiotherapy plus amifostine" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Quote: "open label".
Blinding (performance bias and detection bias) Patients	High risk	Quote: "open label".

Veerasarn 2006 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "open label".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	67 patients randomised. 5 patients (5/35 patients control group) excluded because they were missing baseline data
Selective reporting (reporting bias)	Unclear risk	Data presented in percentages for number of patients with mucositis (> grade 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Veness 2006

Methods	Randomised, parallel group study conducted in Australia. Clear information on withdrawals: 10 (4/42 misoprostol, 6/41 placebo). Dentist involved in study. Duration: until grade 1 or less mucositis was recorded
Participants	Adults with head and neck cancer radiotherapy (n = 52) or concomitant chemotherapy and radiotherapy (n = 31). All patients had > 50% of the oral /oropharyngeal mucosa in the radiation field and received > 50 Gy
Interventions	2 groups, placebo tablets versus misoprostol tablets (200 μg) dissolved in 15 ml of water. Patients asked to swish liquid around the oral cavity for 2 minutes and gargled before being swallowed
Outcomes	Mucositis assessed weekly using a 0-4 scale. Other reported outcomes: quality of life, weight loss, hospital admission, pain,
Notes	Data used from table 3 (incidence of mucositis). Data treated as provided the wrong way round, as the text suggests that 42 patients were received into the misoprostol group and 41 into the placebo group, while the table provides data for 42 placebo patients and 41 misoprostol patients Funding source: government.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomisation was carried out using stratified minimization" Comment: minimization. Authors give information about which factors used for stratification

Veness 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "the patient's mucositis grade was scored by an experienced head and neck clinic nurse on a weekly basis. She had no prior knowledge of patient randomisation" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	83 patients randomised. 10 patients withdrew (4/42 misoprostol, 6/41 placebo). Mucositis data presented for 83 patients
Selective reporting (reporting bias)	Low risk	Data presented for incidence of mucositis by grade and arm (table 3) for 83 patients
Other bias	Low risk	Study appears to be free from other sources of bias.

Vokurka 2005

Methods	Randomised, parallel group, multicentre study conducted in Czech/Slovak Republics between January 2002 and June 2004. Unclear whether assessors blind. Unclear information on withdrawals: 3 refused after start, 2 lost. Unclear if dentist involved in study. Drop outs: 4%. Duration: 28 days, total in-patient stay
Participants	Adults. Disease unclear. BMT. High dose chemotherapy followed by autologous peripheral stem cell transplantation. 137 enrolled and randomised, 132 completed
Interventions	2 groups, placebo (saline) versus povidone iodine (betadine 1 ml and 100 ml water freshly made every morning) (1:100 mouthwashes after high-dose chemotherapy comprising BEAM or HD-L-PAM), patients gargled 4 times a day
Outcomes	Mucositis assessed once daily using the WHO grading on a scale of 0-4. Assessment used: up to 28 days. Other reported outcomes: oral pain, tolerability of mouthwashes, occurrence of infections, fever and oral microbiology in patients with clinical suspicion of local infection
Notes	Funding source: unclear.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "prospective, randomised, multicentre study". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Only patients were blinded to the treatment allocation. Authors give no information on who made up the solutions each morning
Blinding (performance bias and detection bias) Patients	Unclear risk	Quote: "their composition was blinded to the patients." Comment: normal saline versus povidone-iodine. Likely that patients would be able to tell the difference between the treatments. Presumably iodine solution would be orange
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Incomplete outcome data (attrition bias) All outcomes	Low risk	132 patients recruited. 5 patients excluded. Authors give reasons for attrition/ exclusion, but do not state which arms patients were allocated to
Selective reporting (reporting bias)	Low risk	Data presented in percentages for grades of mucositis for both arms of the study (fig 1) , and for incidence of maximum mucositis severity (fig 2/3)
Other bias	High risk	Patients in the povidone group received significantly more cycles of chemotherapy in the year prior to ASCT than the normal saline group (P = 0.01)

Wahlin 1989

Methods	Randomised, parallel group study conducted in Sweden. Clear information about withdrawals: 4/14 control, 3/14 test. Dentist involved in study. Drop outs: 0%. Duration: 21 days
Participants	Children and adults with acute leukaemia at start of chemotherapy. 28 patients enrolled, 14 patients completed (although mucositis data presented on 28)
Interventions	2 groups: no treatment versus chlorhexidine (0.2% 10 ml twice daily)
Outcomes	Mucositis scored at the level of ulceration. Assessment used: day 28. Other reported outcomes: candidiasis verified by detecting pseudohypae in smears, days fever, plaque, gingival bleeding, burning sensation
Notes	Funding source: government.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "28 patients were randomly divided into 2 groups". Quote: "randomisation was performed by means of the closed envelope method in blocks of 6" Comment: unclear if envelopes were shuffled. Random component not described
Allocation concealment (selection bias)	Unclear risk	Quote: "Closed envelope method". Comment: unclear if envelopes were sequentially numbered.
Blinding (performance bias and detection bias) Carers	High risk	Chlorhexidine versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Patients	High risk	Chlorhexidine versus no intervention. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Chlorhexidine versus no intervention. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	28 patients randomised. Data from 7 patients excluded. 3/14 chlorhexidine, 4/14 control group. Authors give reasons for withdrawals and exclusions

Selective reporting (reporting bias)	Unclear risk	Ulceration data presented for 17 patients (table 4).
Other bias	High risk	Blocked randomisation in an unblinded study.

Wang 2002

Methods	Randomised, parallel group study conducted in China. Unclear information about withdrawals, although there appeared to be none. Dentist not involved in study. Drop outs: 0%. Duration: 1 week after course of chemotherapy
Participants	Adults with solid cancer (breast, lung and lymphoma). CHOP for malignant lymphoma, CMF for breast cancer and CAP for lung cancer. 147 eligible and enrolled, and with data
Interventions	2 groups, Dobell's solution as control (30 ml for 3 min, gargling 5 times per day). Concoction of Chinese medicine including 5 herbs (corktree bark, Chinese gaul, European vebena herb, catechu, forsythia fruit) and borneol (sucked and gargled 5 times per day)
Outcomes	Mucositis scored on 4-point scale. Time of healing ulcers.
Notes	Funding source: none. All information is from translation from Chinese

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Intervention and control were different in terms of colour, smell, and style of packaging
Blinding (performance bias and detection bias) Patients	High risk	Intervention and control were different in terms of colour, smell, and style of packaging
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Wang 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	147 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for 147 patients by grade and arm. However, it is unclear over what time interval
Other bias	High risk	Risk of bias assessed from translation.

Watanabe 2010

Methods	Randomised parallel group study conducted in Japan. Open study. No blinding. Clear information about withdrawals: none
Participants	31 adults with head and neck cancer. Recruitment ran from January 2009 until October 2009. 21 patients received chemoradiotherapy. Remaining 9 patients received radiotherapy only. Difference between arms non-significant
Interventions	2 groups. Polaprezinc (zinc-L-carnosine) granules (0.5 g dissolved in 20 ml of 5% sodium alginate solution) compared to azulene oral rinse (7 drops of 4% liquid in 100 ml water). Patients rinsed with solution for 3 minutes 4 times daily. Polaprezinc solution swallowed
Outcomes	Mucositis assessed weekly using Common Terminology Criteria for Adverse Events (CTCAE). Other reported outcomes: pain, xerostomia, taste disturbances, reduction in the use of analgesics, number of patients experiencing inability to intake orally, reduction in daily meals
Notes	Funding source: no information (e-publication ahead of print)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Quote: "open trial". Comment: polaprezinc compared to azulene control.
Blinding (performance bias and detection bias) Patients	High risk	Quote: "open trial". Comment: polaprezinc compared to azulene control.

Watanabe 2010 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "open trial". Comment: polaprezinc compared to azulene control.
Incomplete outcome data (attrition bias) All outcomes	Low risk	31 patients recruited. No missing outcome data.
Selective reporting (reporting bias)	Low risk	Data presented for 31 patients by treatment arm and grade of mucositis
Other bias	High risk	Baseline imbalance: mean serum creatinine values lower in the control arm compared to the polaprezinc arm (P = 0.006).

Wijers 2001

Methods	Randomised, parallel group study conducted in The Netherlands. Unclear information about withdrawals. Dentist involvement unclear. Drop outs: 32%. Duration: 3 weeks after radiation
Participants	Adults with head and neck cancer. 114 patients enrolled, 37 refused to continue, 77 completed
Interventions	2 groups, placebo versus PTA paste containing antibiotics, polymyxin E, tobramycin, amphotericin
Outcomes	Mucositis scored weekly, 5 point scale, Van der Schneren system. Assessment used: day 28 min. Other reported outcomes: pain, microflora
Notes	Funding source: unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to PTA or placebo paste". Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.

Wijers 2001 (*Continued*)

Blinding (performance bias and detection bias) Patients	Low risk	Quote: "double blind". Comment: probably done.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "double blind". Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	114 patients randomised. 37 patients withdrew during the first 4 weeks of the trial (32.5%). Authors give incomplete randomisation and withdrawal information. 77 patients included in efficacy analysis
Selective reporting (reporting bias)	Low risk	Data presented for mucositis grade at week 4 (77 patients) by grade for both groups (table 2). Authors also present data for max mucositis grade and moment of max mucositis grade (table 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

Wu 2009

Methods	Randomised, parallel group study conducted in Korea between January 2007 and August 2007. Unclear if dentist involved in study. Withdrawal information included
Participants	Adults with head and neck cancer receiving radiotherapy. 116 patients were screened. 3 refused to participate, 113 were randomised. 13 patients dropped out before the 5th week of radiotherapy so the endpoint evaluation was only done on 100 patients, 6 because of interruption of radiotherapy for more than 2 consecutive days, 3 for receiving prohibitive drug treatments, 2 for refusal to participate, 1 because of adverse effects of radiotherapy, 1 for not being treated with the test drug
Interventions	Patients were randomised to 1 of 4 arms: placebo, epidermal growth factor 10 μg/mL, 50 μg/mL or 100 μg/mL. Epidermal growth factor and placebo both administered as a spray over the entire oral mucosa, twice daily with patients swallowing the residual. Treatment from day 1 to day 5 of radiotherapy
Outcomes	Mucositis scored weekly using RTOG scoring criteria. Assessment used: day 28. Other reported outcomes: WHO oral toxicity grade, patient weight, pain score, opioid analgesia use and time to develop mucositis
Notes	Funding source: grant from the National R&D Program for Cancer Central, Ministry of Health, Welfare and Family Affairs, Republic of Korea
Risk of bias	

Wu 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "We randomised patients to institution and concurrent use of chemotherapy" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Quote: "double blind". Comment: possible patient knowledge of allocation. Therefore all blinding deemed inadequate
Blinding (performance bias and detection bias) Patients	High risk	Quote: "double blind". Comment: authors state that 1 patient dropped out because they were not randomised to the test drug. Patient knowledge of allocation. Therefore blinding judged to be inadequate
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "double blind". Comment: possible patient knowledge of allocation. Therefore all blinding deemed inadequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	70 patients randomised (1/28 control group, 3/29 10 µg/mL arm, 3/29 50 µg/mL arm, 5/27 100 µg/mL arm). No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Data presented in text for percentage of patients with oral mucositis > RTOG grade 3. Data also presented for average grade of mucositis by week for patient treated with 50 mg/mL compared with placebo (fig 4)
Other bias	Low risk	Study appears to be free of other sources of bias.

You 2009

Methods	Randomised, parallel group study conducted in Taiwan. Clear information about withdrawals. Unclear if dentist involved in study. Drop outs: 9%. Duration: 1 week after course of chemotherapy
Participants	Adults with head and neck cancer receiving radiotherapy. 22 patients randomised to 2 groups enrolled between October 2005 and May 2006. 2 patients in control withdrew due to refusal to give blood sample
Interventions	2 groups, saline and indigo wood root (IR) (Isatis indigotica called Ban-Lan-Gen in Chinese is a medicinal plant belonging to the Brassicacaee family). Patients gargled with 30-mL solution of either saline or IR for 3 minutes and then swallowed before meals daily
Outcomes	Mucositis scored on 4-point scale. Time of healing ulcers. Also reported difficulty swallowing, anorexia, rest from treatment, blood changes
Notes	Funding source: none.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were sequentially randomised into two treatment arms: (I) indigowood root group: 0.5g IR powder in 30mL double distilled water; (II) Control group: placebo with 30mL normal saline" Comment: random component not described.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Patients	Unclear risk	Indigo wood root or placebo. No apparent blinding.
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Indigo wood root or placebo. No apparent blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	22 patients were randomised. 2 patients withdrew from the placebo group. 20 patients included in analysis.

Selective reporting (reporting bias)	Low risk	Data presented for 20 patients for mucositis incidence by arm and treatment
Other bias	High risk	All Chinese medicine RCTs are now a cause for concern in light of the findings of Taixiang et al 2007

Yuen 2001

Methods	Randomised, parallel group study conducted in Hong Kong. Clear information on withdrawals: none. Unclear if dentist involved in study. Drop outs: 0%. Duration: 60 days after BMT
Participants	Adults with mixed cancer receiving BMT, 70 enrolled between October 1996 to February 1998. 70 evaluated
Interventions	2 groups no treatment versus clarithromycin oral 500 mg twice daily or IV 500 mg 12 hourly. Start day -7
Outcomes	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
Notes	Funding source: none.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The 70 patients were randomly divided into 2 subgroups by computer" Comment: computer generated randomisation.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding (performance bias and detection bias) Carers	High risk	Quote: "open-label". Comment: no blinding.
Blinding (performance bias and detection bias) Patients	High risk	Quote: "open-label". Comment: no blinding.
Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "open-label". Comment: no blinding.

Incomplete outcome data (attrition bias) All outcomes	Low risk	70 patients randomised. No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Data presented for grade 0-1 and grade 2 mucositis (table 2)
Other bias	Low risk	Study appears to be free of other sources of bias.

ASTC = autologous stem cell transplantation
BMT = bone marrow transplant
EORTC = European Organization for Research and Treatment of Oral Cancer
GI = glycaemic index
GM-CSF = granulocyte/macrophage colony-stimulating factor
GVHD = graft-versus-host disease
HSCT = haematopoietic stem cell transplant
HSV = herpes simplex virus
ITT = intention-to-treat analysis
IV = intravenous
KGF = keratinocyte growth factor
NCI CTC = National Cancer Institute Common Toxicity Criteria
OAG = oral assessment guide
OM = oral mucositis
OMAS = oral mucosa assessment scale
OMS = objective mucositis score
ROB = risk of bias
RT = radiotherapy
RTOG = Radiation Therapy Oncology Group
SD = standard deviation
SOC = standard oral care
TBI = total body irradiation
TPN = total parenteral nutrition
UOM = ulcerative oral mucositis
VAS = visual analogue scale
WBC - white blood count
WHO = World Health Organization
5-FU = 5-fluorouracil
(c) indicates from correspondence with authors.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abramoff 2008	Patients considered new case and re-randomised for each CT cycle (laser versus no treatment)
Aisa 2005	Not RCT (cryotherapy).
Altmann 1999	Not RCT (amifostine).
Andersen 1987	Cancer treatments comparing toxic effects.
Anderson 1998b	Mucositis at baseline in some patients (glutamine versus placebo)
Antin 2002	Study stopped early due to adverse event triggering preset stopping rule - data only for 10 patients in rhIL group and 3 placebo (rhIL-11 versus placebo)
Antonadou 1998	Abstract, insufficient information (radiotherapy with or without GM-CSF)
Apaydin 1996	Unclear whether allocation is randomised.
Aquino 2005	Composite score for mucositis including teeth with plaque (Walsh). Unable to use mucositis outcome outcomes (oral glutamine)
Ardizzoni 2002	Cancer treatments comparing toxic effects and confounded by cancer (G-CSF)
Arora 2008	Not RCT (laser).
Awada 2002	Cancer treatment comparing toxic effects.
Awada 2004	Not RCT (temozolomide plus liposomal doxorubicin).
Awidi 2001	Episodes not patients. Type of cross-over study but some patients were included in more than 2 'courses' (pilocarpine versus placebo)
Awwad 2002	Cancer treatments comparing toxic effects (conventional fractionation versus accelerated hyperfractionation radiotherapy)
Barasch 1995	As patients had already received some chemotherapy before intervention started, some patients, but not all, have some mucositis. The trial is therefore a combination of prevention and treatment (He-Ne laser versus no treatment)
Baydar 2005	Not RCT (cryotherapy).
Bensadoun 2006	Comparison of different cancer treatment regimens, not primary outcome
Bentzen 2001	Comparing different chemotherapy regimens.

(*Continued*)

Bleehen 1996	Different chemotherapy regimens.
Bourhis 2006	Comparing 2 radiotherapy regimens but looking at toxicity.
Braaksma 2002	Email sent to author requesting further information; no reply received by March 2011
Buentzel 1999	Abstract - insufficient information (amifostine).
Calais 2000	Trial of cancer treatments.
Calais 2004	Not RCT (chemotherapy).
Cassidy 2002	Cancer treatments comparing toxic effects.
Castro 2009	Abstract.
Cella 2003	Emailed authors Nov 17 2010 requesting data to include this study in review. Authors replied stating that data held by pharma company and no longer available
Cheng 2001	Not RCT (oral care protocol).
Cheng 2002	Not RCT (oral care protocol).
Cheng 2006	Grade 2 mucositis was an exclusion criteria. However, unclear how many patients had grade 1 mucositis at baseline. Email sent to authors. No reply
Clarke 2001	Abstract, insufficient information (rHuKGF).
Colella 2010	Open non-randomised trial.
Collova 2004	Abstract - insufficient information.
Colombat 1995	Abstract - insufficient information (fluconazole versus amphotericin B)
Costa 1999	Abstract, not RCT (chlorhexidine versus no treatment).
Costa 2003	Not RCT (chlorhexidine versus control).
Cowen 1997	Daily mucositis index used and summed across all categories (including voice, saliva). A cumulative oral mucositis score generated for both nursing and patient assessments was used and categorised into a 0-3 mucositis scale. Daily mucositis index ranging from 0-48 used, with means (SD) presented but excluded as composite scale (He-Ne laser versus no treatment)
Cunningham 1995	Investigating new cancer treatment, tomudex, with oral mucositis as one of the minor side effects
Damon 2004	Trial investigating 2 different methods of administering etoposide

(*Continued*)

De Boer 2002	Cancer treatments comparing toxic effects (conventional versus accelerated infusional chemotherapy)
Denham 1999	Cancer treatments comparing toxic effects (conventional versus accelerated fractionation)
Djuric 2006	Some mucositis present at baseline.
Dobrowsky 1998	Added to speed up radiotherapy, not radio-protection-toxic (mitomycin)
Doroshow 1987	Cancer treatments comparing toxic effects.
Dreicer 1997	Not RCT(edatrexate).
Dudjak 1987	Uses Beck's OAG mucositis score (includes ability to swallow, saliva, diet and patient ability to self care) (2 oral care protocols)
Edelman 1998	Not RCT (cryotherapy).
Eisen 2003	Not RCT (valacyclovir versus acyclovir).
El-Sayed 2002a	Not RCT (antimicrobial lozenge).
Epstein 1992	Sum of composite self-reported scale including mouth pain and its effect on oral intake, and the absence or presence of stomatitis. Unable to use in review (3 groups: chlorhexidine rinse, nystatin suspension and saline solution)
Erkisi 1996	Patients randomised to different cancer treatments and where given G-CSF when clinically indicated, not randomly allocated (G-CSF versus no treatment)
Erlichman 1988	Comparing different chemotherapy regimens.
Etiz 2000	Multicomponent scale of mucositis including pain, dysphasia and use of systemic analgesics (sucralfate versus placebo)
Ezzat 2005	Comparing 3 different radiotherapy regimens, survival not mucositis is primary outcome
Fahlke 1999	Not RCT (amifostine).
Falcone 2001	Comparing different radiotherapy regimens.
Fay 1994	Not RCT (GM-CSF).
Feber 1995	Oral assessment guide not just mucositis but includes plaque and voice changes (hydrogen peroxide versus sodium chloride rinses)
Feber 1996	Oral assessment guide not just mucositis but includes plaque and voice changes (2 oral care protocols)

(*Continued*)

Ferreira 2004	Email sent to authors Nov 2010 requesting sufficient information to include study in this review. No reply received March 2011
Ferretti 1990	Patients had mucositis at baseline.
Foncuberta 2001	Patients assigned sequentially not RCT (GF-B3).
Gabison 1995	Abstract - insufficient information (zinc picolinate).
Gandara 1997	Not RCT (edatrexate).
Genot-Klastersky 2008	Some patients had grade 1 mucositis in prevention trial (laser versus placebo)
Ghoreishi 2007	Email sent to authors Nov 2010 requesting further information to enable this study to be included. No reply received by March 2011
Giles 2003a	Comparing chemotherapy regimens not mucositis interventions.
Giles 2003b	Cancer treatment toxicity (troxacitabine).
Gladkov 2007	Comparing different radio-chemo regimes for oral cancer.
Goldberg 2003	Abstract - insufficient information (en3247).
Gordon 1993	Abstract, insufficient information (GM-CSF).
Grotz 2001	Index not in suitable form. Total RTOG scores including salivary glands, mucosa, skin (comarin/troxerutine versus placebo)
Gutierrez 1996	Not RCT (fluconazole).
Harris 1995	Abstract, insufficient information (folinic acid mouthwash versus placebo)
He 2004	Abstract - insufficient information (amifostine).
Hickey 1982	Problems with data. 21 patients in total, unclear how many patients per group, but data presented as 67 courses of chemotherapy (oral hygiene protocols)
Horsley 2007	Not RCT (keratinocyte).
Howell 1983	Unclear if randomised. Cross-over study provided 59 paired course of treatment in 23 patients (allopurinol)
Hu 2003	Not RCT (amifostine).
Hunter 2007	Not RCT. This study combines patients who were in cohorts with increasing doses of mouthrinse to assess safety, with an RCT (ATL-104 mouthwash versus placebo)

(*Continued*)

Hwang 2004	Email sent to authors Nov 2010 requesting further details concerning this study. No reply was received by March 2011
Inagaki 2006	Not RCT (cryotherapy).
Ito 2002	Not RCT (allopurinol spray).
Jebb 1995	Index of mucositis had multiple components other than mucositis (glutamine versus placebo)
Jham 2007	Study for prevention of xerostomia (bethanechol versus saliva supplement)
Johnson 2002	Not RCT (prostaglandin e1).
Ju 2009	Quasi-randomised study. Patients alternatively allocated to intervention and placebo
Kante 1995	Abstract - insufficient information (oral care regimens).
Karacetin 2004	Patients were 'randomised' to intervention or control according to file number (amifostine versus no treatment)
Karthaus 1998	Problems with the data. 8 patients, 32 chemo cycles and results presented assuming independent (G-CSF versus placebo)
Kenny 1990	Oral assessment guide not only mucositis but includes plaque and voice changes (2 oral care protocols)
Khouri 2009	Quasi-randomised study. Patients allocated to intervention and placebo alternatively based on date of hospitalisation
Klocke 2006	Abstract - insufficient information.
Kuhn 2009	Children had mucositis grades 2+ on entry into trial.
Kuriakose 2002	Not RCT (edatrexate).
Labbate 2003	Not RCT.
Lanzos 2010	7 patients had mucositis at baseline (including 2 patients with grade 4 mucositis)
Lavendag 1998	Abstract, insufficient information (polyenes versus placebo)
Le 2008	Abstract (keratinocyte growth factor).
Lee 1989	Intervention given as part of cancer treatment, not to prevent mucositis
Leong 1995	Abstract, insufficient information (thymidine versus no treatment)

(*Continued*)

Levi 1997	Comparison of 2 cancer treatments where the primary outcome was maximum tumour response to therapy
Loo 2010	130 of the 139 patients recruited into the study had mucositis at baseline
Lopez 1994	Data presented as number of days patients suffered for each grade of mucositis. Cannot be used in meta-analysis unless we obtain further information from authors. Unable to contact authors
Lopez-Campo 2004	Abstract only. Insufficient information to include in review. No subsequent publication identified (March 2011)
Lorusso 2003	Episodes not patients considered in analysis (amifostine).
Lozada 1998	Abstract with insufficent information given (pilocarpine).
Luglié 2002	Not RCT.
Maddocks-Jennings 2009	Not RCT (alternate allocation and if patient could not gargle they were re-allocated to other groups) (essential oils)
Madero 1999	No response to query whether patients were randomised to groups (rhGM-CFS)
Mahmoud 1996	Comparison of 2 cancer treatments where the primary outcome was survival (folinic acid)
Malaker 1991	Not RCT (B-Carotene retinoic acid).
Mantovani 2003	Not randomised.
Marcial 1994	Abstract, insufficient information. It states it is an RCT but mentions historical control group (low energy laser versus no treatment)
Martin 2006	Not RCT (G-CSF).
Masucci 2005	Treatment of mucositis not prevention.
Matejka 1990	Not RCT (prostaglandin E2).
McIlroy 1996	Scoring system incorporated visible signs of mucositis with pain dysphasia and weight loss. Qualitative assessment with no data given (polyenes versus placebo)
Merte 1999	Abstract (German).
Mills 1995	Not RCT.
Mori 2006	Not RCT (cryotherapy).
Nicolatou-Galitis 2006	Not an RCT. Patients who received the intervention were compared to a control cohort

(*Continued*)

Niibe 1985	Report in Japanese. Translator describes outcome as oral mucous symptoms, time of assessment unclear (based on radiation dose delivered) and reported as percentages per group with no denominators or estimate of precision. Insufficient information to include and study to old to be able to contact authors (amifostine versus placebo)
Nikoletti 2005	Cross-over study, some doubt as to whether patients had any mucositis at baseline and outcomes used OAG assessment scale which is an exclusion criterion for this review
Okuno 1997	Major change to protocol half way through study (antibiotic lozenge versus placebo). Data from blinded and unblinded patients combined. Chlorhexidine for first part included as study by Foote 1994. Data from first part comparing antibiotic lozenge with placebo mouthrinse have not been included as we feel this is an inappropriate control
Okutomi 2000	Not RCT (Z-100 injections).
Papadeas 2007	CCT (cryotherapy).
Papas 1984	Abstract (patient management system).
Papas 2003	The interventions were calcium phosphate rinses plus fluoride tray applications versus fluoride rinses + placebo tray applications. The individual interventions were confounded
Penpattanagul 2007	Not RCT. "Patients were assigned to their treatment groups at the discretion of the investigator with an attempt to achieve equal distribution of patient demographics."
Peters 1993	CCT. Paper states "Randomisation procedure was done according to day of birth."
Phillips 2002	Not RCT (amifostine).
Piccirillo 2003	Excluded as mucositis index inappropriate for review. Mucositis index included pain and difficulty in swallowing (response from authors)
Pouli 1999	Abstract, insufficient information (GM-CSF versus sodium bicarbonate mouthwash)
Prada 1985	Mucositis present at baseline (benzydamine versus placebo mouthwash)
Putwatana 2009	Quasi-randomised trial. Patients allocated to the intervention (glycerin payayor) or control (benzydamine) by alternative allocation
Pyrhonen 1995	Mucositis not primary outcome. Only presents data for test arm as adverse event (chemotherapy agents)
Pytlik 2002	Inappropriate mucositis index includes voice quality and teeth (glutamine versus placebo)
Rabinovitch 2006	Trial of radiotherapy for head and neck cancer looking at cancer treatment
Rades 2004	Study halted when preset stopping rules were triggered due to adverse effects of amifostine. No mucositis outcomes reported (amifostine)

(*Continued*)

Radmard 2002	Abstract - insufficient information (rhGM-CSF).
Raether 1989	Average mucosal rating presented without standard deviation. Cannot be used in meta-analysis unless we obtain further information from authors. Unable to contact authors
Robustelli 1999	Abstract - insufficient information (galenic preparation).
Rocci 2005	Not eligible since it is not dealing with prevention or treatment of mucositis, but uses mucositis to measure side effect of 2 different ways to deliver an antitumoural drug for the treatment of gastrointestinal tumours
Rojas 2001	Episodes not patients.
Rothwell 1990	Mucositis scores presented as means. Oral screening tool includes moniliasis (candidiasis)
Rutkauskas 1993	No data for mucositis presented by randomised group, just line graph of all patients with no P values (chlorhexidine versus placebo)
Ryu 2007	6% of patients had oral mucositis at baseline.
Samaranayake 1988	Average mucosal rating presented without standard deviation. Cannot be used in meta-analysis unless we obtain further information from authors. Unable to contact authors
Sato 1997	Unsure if RCT and author has not responded to letter requesting further information
Sato 2006	Not RCT (cryotherapy).
Schuster 2008	Not RCT (velafermin).
Schwerkoske 1999	Abstract, insufficient information (rhIL11).
Shabanloei 2009	Quasi-randomised study. "Patients selected based on their ID code and by choosing from the box and were divided into three groups."
Sharma 2009	Abstract.
Shea 2007	Abstracts only, insufficient information (palifermin).
Shidfar 2008	Abstract.
Simoes 2009	Not RCT (laser).
Spadaro 1991	Abstract, insufficient information (vitamin E + vitamin A + fluconazole versus no treatment)
Spielberger 2001	Abstract, insufficient information (keratinocyte).
Stokman 2004	Not RCT. This was a cross-over study but not randomised. All patients had control cycle first

(*Continued*)

Teshima 1986	Japanese paper. Unclear information as to whether this was randomised. Written to authors but no reply
Thieblemont 2002	Not RCT.
Throuvalas 1995	Abstract, probably not RCT described as comparative study (GM-CSF)
Tiemann 2006	Not RCT (herbs).
Toubai 2003	Probably not RCT, only 12 patients in total? (itraconazole).
Uchiyama 2005	Not RCT.
Valcarcel 2002	Participants had mucositis at baseline.
Valcárcel 1997	Abstract - insufficient information (thymostimulin).
van Zaanen 1994	Patients randomised per treatment cycle, 15 patients and 20 treatments cycles. Patients randomised up to 3 times, data treated as independent but not reported per patient (glutamine + TPN versus standard TPN)
Verdi 1995	Mucositis measured by OAG which includes teeth. Only in 10 patients (pentoxifylline versus placebo)
Vesole 1999	Abstract insufficient information (IB-367).
Villar 2009	Abstract.
Vitello 2000	Abstract, insufficient information (lidocaine versus dyclone mouthrinses)
Wagner 2002	Abstract for treatment of mucositis review (GM-CSF).
Wang 2002a	Not RCT.
Ward 2007	CCT (glutamine).
Warde 2002	Maximal toxicity during treatment presented as percentages. Cannot be used in meta-analysis unless we obtain further information from authors. Email sent 17 Nov 2010, no reply received by March 2011
Weisdorf 1989	Outcome data presented as graph with standard deviations. Cannot be used in meta-analysis unless we obtain further information from authors. Unable to contact authors
Weiss 1990	Not randomised. Cross-over trial and data in wrong form for review (allopurinol)
Whelan 2002	Not RCT.
Whelan 2004	Not RCT (from author).
Wollina 2002	Not RCT (dexpanthenol).

(*Continued*)

Wymenga 1999	Not RCT (TGF-B3 mouthrinse versus no treatment).
Yokomizo 2004	Not RCT.
Zanin 2010	Mucositis data presented as mean values. Unclear if randomised. Authors contacted - no reply

CCT = controlled clinical trial; CT = chemotherapy; RCT = randomised controlled trial; SD = standard deviation.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Cheng 2003

Methods	Randomised cross-over comparison of chlorhexidine versus benzydamine oral care protocols
Participants	Children aged 6-17 undergoing chemotherapy recruited between April 2000 and April 2001
Interventions	2 groups, oral care protocol based on chlorhexidine mouthrinse twice daily during chemotherapy compared to an oral care protocol based on benzydamine twice daily
Outcomes	WHO mucositis scores, oral symptoms (eating, chewing, swallowing, speaking, mouth dryness on VAS scale), pain, use of analgesics, concomitant medications
Notes	3 publications relating to the same study. Unclear whether any patients had oral mucositis at baseline. Email sent to authors requesting clarification

de Koning 2007

Methods	Randomised, cross-over study conducted in The Netherlands.
Participants	Children with haematological malignancies receiving chemotherapy
Interventions	2 groups, placebo feeds versus TGF-2 enriched feeds (dose dependant on patient weight)
Outcomes	Mucositis assessed daily using the WHO scale. Other reported outcomes: diarrhoea, pain, use of analgesics, administration of antibiotics, frequency of blood cultures
Notes	Discrepancy between data presented in tables 2 & 3 in the paper. Awaiting clarification of data from authors

Grzegorczyk 2006

Methods	Randomised, parallel group study conducted in Poland.
Participants	Adults undergoing stem cell transplantation.
Interventions	2 groups, placebo (methylcellulose) versus G-CSF (300 μg in 2% methylcellulose)
Outcomes	Mucositis assessed using the WHO score. Other reported outcomes: granulocytes, patient report of pain
Notes	Translation provided insufficient information. Discrepancy between graph legends and descriptions. Awaiting more information from translators

Jellema 2006

Methods	Randomised, parallel group study conducted in The Netherlands. Clear information about withdrawals: 0. Unclear if dentist involved in study. Recruitment took place between August 1999 and August 2003
Participants	Adults with head and neck cancer undergoing radiotherapy.
Interventions	3 groups, no treatment control versus amifostine (200 mg/m^2) 5 times weekly versus amifostine (200 mg/m^2) 3 times weekly. Amifostine administered 15-30 minutes before irradiation
Outcomes	Unclear how mucositis was assessed. Other reported outcomes: xerostomia, patient quality of life, sticky saliva, locoregional control and survival
Notes	Discrepancy between legend for Figure 2 and the text in this paper. Email sent. Awaiting clarification from authors

Peterson 2007

Methods	Randomised, multicentre cross-over study conducted in Russia. Dentist involved in study. Duration: randomised to glutamine versus placebo in cycle 1 and then crossed over to alternative treatment in cycle 2
Participants	Adults with breast cancer receiving chemotherapy.
Interventions	Glutamine versus placebo.
Outcomes	Mucositis on OMAS scale. Mean score calculated as mean ulceration score across all sites. Mean erythema score similarly calculated. Also WHO score assessed. Other outcomes: nausea, vomiting, dry mouth
Notes	Eligible if experienced WHO mucositis $\geq$ 2 during screening cycle. Percentage of patients with WHO scores $\geq$ 2 presented 1 to 21 days in graph for each group during cycle 1. Significant carry-over effect from cycle 1 to cycle 2. Need to obtain further information from authors

Wu 2010

Methods	Randomised, parallel group study conducted in China. Recruited between February 2006 and May 2007
Participants	Patients with nasopharyngeal carcinoma undergoing chemoradiotherapy
Interventions	3 groups; actovegin from start of chemo, actovegin from time of grade 2 mucositis, versus no treatment
Outcomes	NCI-CTC mucositis scale, pain, weight loss, adverse events.
Notes	Full text paper published October 2010. To be included in next update

Yasuda 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Zhe 2000

Methods	
Participants	
Interventions	
Outcomes	
Notes	

BMT = bone marrow transplant; G-CSF = granulocyte colony-stimulating factor; NCI-CTC = National Cancer Institute - Common Toxicity Criteria; OMAS = oral mucosa assessment scale; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; VAS = visual analogue scale; WHO = World Health Organization.

DATA AND ANALYSES

Comparison 1. Allopurinol versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	4		Risk Ratio (Random, 95% CI)	0.77 [0.50, 1.19]
2 Mucositis (moderate plus severe)	2	54	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.50, 0.86]
3 Mucositis (severe)	2	54	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.63, 1.04]

Comparison 2. Aloe vera versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (moderate plus severe)	2	119	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.58, 0.96]

Comparison 3. Amifostine versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	3	430	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 0.99]
2 Mucositis (moderate plus severe)	6	757	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.58, 0.96]
3 Mucositis (severe)	9	845	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.45, 1.03]

Comparison 4. Chlorhexidine versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	4	454	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.47, 1.24]
2 Mucositis (moderate plus severe)	3	233	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.21]
3 Mucositis (severe)	4	244	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.54, 1.23]

Comparison 5. Cryotherapy versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	5		Risk Ratio (Random, 95% CI)	0.74 [0.57, 0.95]
2 Mucositis (moderate plus severe)	5		Risk Ratio (Random, 95% CI)	0.53 [0.31, 0.91]
3 Mucositis (severe)	5		Risk Ratio (Random, 95% CI)	0.36 [0.17, 0.77]

Comparison 6. Glutamine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	6		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 Oral suspension/supplementation	5		Risk Ratio (Random, 95% CI)	0.78 [0.57, 1.08]
1.2 IV supplementation	1		Risk Ratio (Random, 95% CI)	0.33 [0.04, 2.63]
2 Mucositis (moderate plus severe)	6		Risk Ratio (Random, 95% CI)	Subtotals only
2.1 Oral suspension/supplementation	5		Risk Ratio (Random, 95% CI)	0.88 [0.69, 1.12]
2.2 IV supplementation	1		Risk Ratio (Random, 95% CI)	0.33 [0.04, 2.63]
3 Mucositis (severe)	8		Risk Ratio (Random, 95% CI)	Subtotals only
3.1 Oral suspension/supplementation	5		Risk Ratio (Random, 95% CI)	0.69 [0.37, 1.29]
3.2 IV supplementation	3		Risk Ratio (Random, 95% CI)	0.25 [0.10, 0.62]

Comparison 7. G-CSF versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	4	263	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.48, 1.23]
2 Mucositis (severe)	2	54	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.86]

Comparison 8. GM-CSF versus no treatment/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	2	119	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.84, 1.04]
2 Mucositis (moderate plus severe)	2	138	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.76, 1.05]
3 Mucositis (severe)	6	373	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.39, 1.40]

Comparison 9. Honey versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	3	120	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.56, 0.88]
2 Mucositis (moderate plus severe)	2	80	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.31, 0.74]
3 Mucositis (severe)	2	80	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.13, 0.52]

Comparison 10. Hydrolytic enzymes versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Mucositis (moderate plus severe)	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 11. Iseganan versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (moderate plus severe)	2	926	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.89, 1.03]
2 Mucositis (severe)	2	926	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.10]

Comparison 12. Keratinocyte GF versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	2	160	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.71, 0.94]
2 Mucositis (moderate plus severe)	7	640	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.89]
3 Mucositis (severe)	6	559	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.58, 0.90]

Comparison 13. Laser versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	3	131	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.71, 1.17]
2 Mucositis (moderate plus severe)	2	97	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.08]
3 Mucositis (severe)	2	97	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.06, 0.62]

Comparison 14. Pilocarpine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	2	276	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [1.00, 1.10]
2 Mucositis (moderate plus severe)	2	276	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.16]

Comparison 15. Povidone versus water

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	2	172	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.76, 1.08]
2 Mucositis (moderate plus severe)	2	172	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.62, 1.10]
3 Mucositis (severe)	2	172	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.40, 1.06]

Comparison 16. Prostaglandin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	3	159	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.94, 1.12]
2 Mucositis (severe)	2	143	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.72, 1.43]

Comparison 17. PTA antibiotic pastille or paste versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	2	298	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.78, 0.96]
2 Mucositis (severe)	2	135	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.09]

Comparison 18. Radiotherapy: am versus pm

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (severe)	2	382	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.85, 1.36]

Comparison 19. Sucralfate versus placebo/usual care

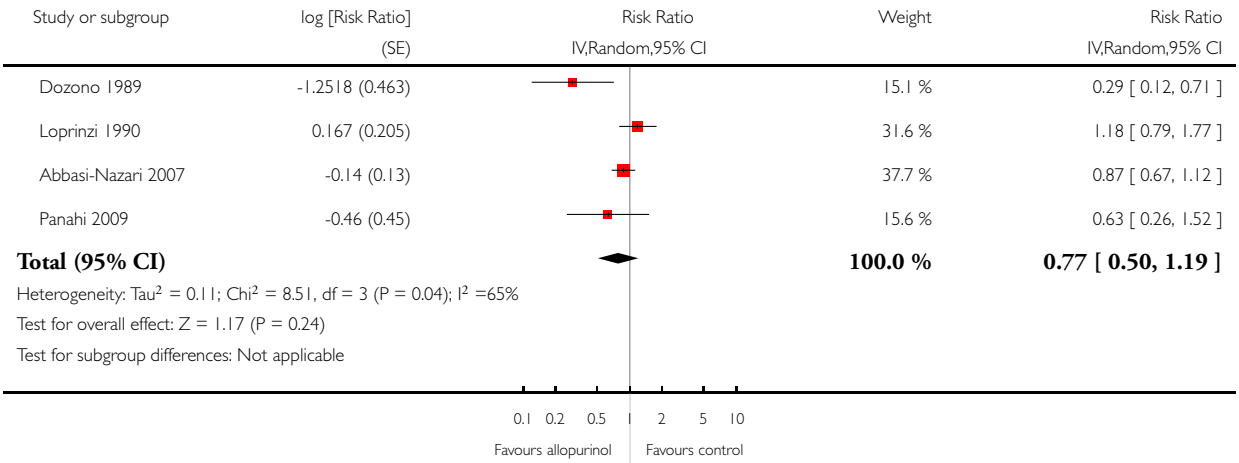
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mucositis (any)	3	222	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.88, 1.10]
2 Mucositis (moderate plus severe)	4	164	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.54, 1.04]
3 Mucositis (severe)	7		Risk Ratio (Random, 95% CI)	0.67 [0.48, 0.92]

Analysis 1.1. Comparison 1 Allopurinol versus placebo/no treatment, Outcome 1 Mucositis (any).

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

Comparison: 1 Allopurinol versus placebo/no treatment

Outcome: 1 Mucositis (any)

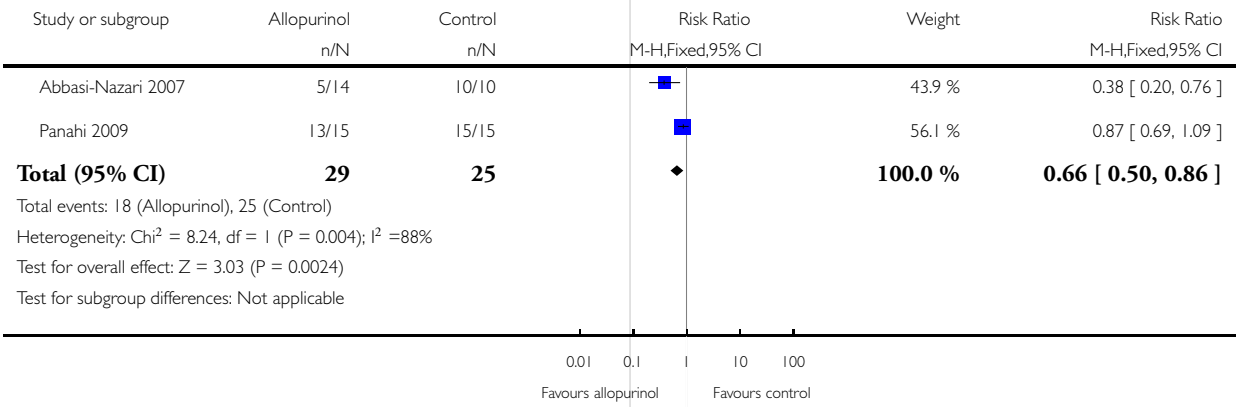


Analysis 1.2. Comparison 1 Allopurinol versus placebo/no treatment, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 1 Allopurinol versus placebo/no treatment

Outcome: 2 Mucositis (moderate plus severe)



Analysis 1.3. Comparison 1 Allopurinol versus placebo/no treatment, Outcome 3 Mucositis (severe).

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

Comparison: 1 Allopurinol versus placebo/no treatment

Outcome: 3 Mucositis (severe)

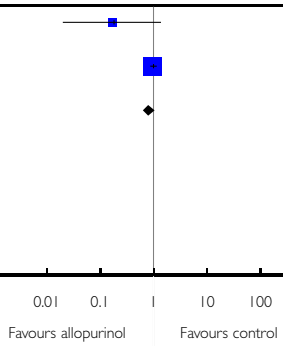
Study or subgroup	Allopurinol n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Abbasi-Nazari 2007	1/14	4/10		23.1 %	0.18 [0.02, 1.37]
Panahi 2009	15/15	15/15		76.9 %	1.00 [0.88, 1.13]
Total (95% CI)	**29**	**25**		**100.0 %**	**0.81 [0.63, 1.04]**

Total events: 16 (Allopurinol), 19 (Control)

Heterogeneity: Chi^2 = 13.14, df = 1 (P = 0.00029); I^2 =92%

Test for overall effect: Z = 1.68 (P = 0.092)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 Aloe vera versus placebo, Outcome 1 Mucositis (moderate plus severe).

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

Comparison: 2 Aloe vera versus placebo

Outcome: 1 Mucositis (moderate plus severe)

Study or subgroup	Aloe vera n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Su 2004	18/28	21/30		43.3 %	0.92 [0.64, 1.32]
Puataweepong 2009	16/30	27/31		56.7 %	0.61 [0.43, 0.88]
Total (95% CI)	**58**	**61**		**100.0 %**	**0.74 [0.58, 0.96]**

Total events: 34 (Aloe vera), 48 (Control)

Heterogeneity: Chi^2 = 2.42, df = 1 (P = 0.12); I^2 =59%

Test for overall effect: Z = 2.27 (P = 0.023)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Amifostine versus placebo/no treatment, Outcome 1 Mucositis (any).

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

Comparison: 3 Amifostine versus placebo/no treatment

Outcome: 1 Mucositis (any)

Study or subgroup	Amifostine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Buntzel 1998	23/25	14/14		6.0 %	0.94 [0.80, 1.09]
Brizel 2000	140/148	152/153		89.6 %	0.95 [0.91, 0.99]
Spencer 2005	34/43	42/47		4.4 %	0.88 [0.74, 1.06]
Total (95% CI)	**216**	**214**		**100.0 %**	**0.95 [0.91, 0.99]**

Total events: 197 (Amifostine), 208 (Control)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.94, df = 2 (P = 0.63); I^2 =0.0%

Test for overall effect: Z = 2.72 (P = 0.0065)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Amifostine versus placebo/no treatment, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 3 Amifostine versus placebo/no treatment

Outcome: 2 Mucositis (moderate plus severe)

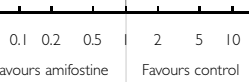
Study or subgroup	Amifostine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Brizel 2000	116/148	130/153		24.4 %	0.92 [0.83, 1.03]
Koukourakis 2000	12/60	38/70		11.2 %	0.37 [0.21, 0.64]
Antonadou 2002	19/22	23/23		22.5 %	0.87 [0.72, 1.04]
Spencer 2005	19/43	32/47		15.6 %	0.65 [0.44, 0.96]
Veerasarn 2006	4/32	14/30		4.9 %	0.27 [0.10, 0.72]
Buentzel 2006	47/65	45/64		21.3 %	1.03 [0.83, 1.28]
Total (95% CI)	**370**	**387**		**100.0 %**	**0.75 [0.58, 0.96]**

Total events: 217 (Amifostine), 282 (Control)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 25.86$, df = 5 (P = 0.00010); $I^2 = 81\%$

Test for overall effect: Z = 2.32 (P = 0.020)

Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3 Amifostine versus placebo/no treatment, Outcome 3 Mucositis (severe).

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

Comparison: 3 Amifostine versus placebo/no treatment

Outcome: 3 Mucositis (severe)

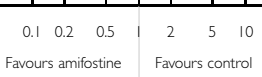
Study or subgroup	Amifostine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Buntzel 1998	0/14	12/14		2.0 %	0.04 [0.00, 0.62]
Bourhis 2000	11/12	11/12		17.2 %	1.00 [0.79, 1.27]
Brizel 2000	52/148	60/153		16.7 %	0.90 [0.67, 1.20]
Koukourakis 2000	1/60	15/70		3.5 %	0.08 [0.01, 0.57]
Hartmann 2001	5/20	10/20		10.0 %	0.50 [0.21, 1.20]
Antonadou 2002	5/22	18/23		10.8 %	0.29 [0.13, 0.65]
Spencer 2005	5/43	15/47		9.6 %	0.36 [0.14, 0.92]
Buentzel 2006	25/65	14/64		13.7 %	1.76 [1.01, 3.07]
Haddad 2009	22/29	20/29		16.5 %	1.10 [0.80, 1.51]
Total (95% CI)	**413**	**432**		**100.0 %**	**0.68 [0.45, 1.03]**

Total events: 126 (Amifostine), 175 (Control)

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 40.39$, df = 8 (P<0.00001); I^2 =80%

Test for overall effect: Z = 1.80 (P = 0.072)

Test for subgroup differences: Not applicable

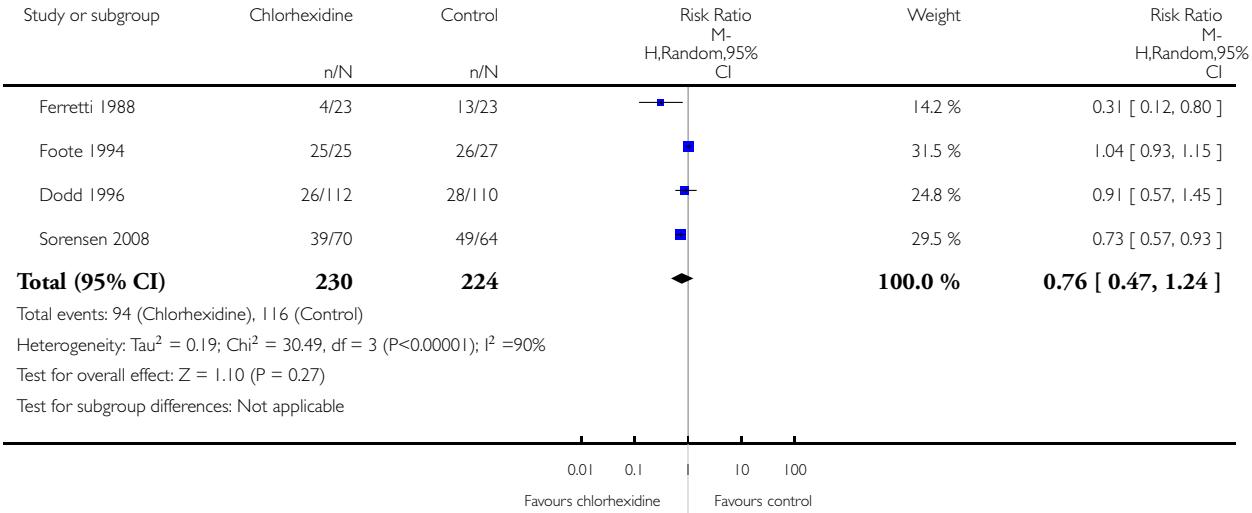


Analysis 4.1. Comparison 4 Chlorhexidine versus placebo/no treatment, Outcome 1 Mucositis (any).

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

Comparison: 4 Chlorhexidine versus placebo/no treatment

Outcome: 1 Mucositis (any)



Analysis 4.2. Comparison 4 Chlorhexidine versus placebo/no treatment, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 4 Chlorhexidine versus placebo/no treatment

Outcome: 2 Mucositis (moderate plus severe)

Study or subgroup	Chlorhexidine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Foote 1994	22/25	21/27		37.0 %	1.13 [0.88, 1.45]
Pitten 2003	9/24	2/23		3.7 %	4.31 [1.04, 17.87]
Sorensen 2008	20/70	31/64		59.3 %	0.59 [0.38, 0.92]
Total (95% CI)	**119**	**114**		**100.0 %**	**0.93 [0.72, 1.21]**

Total events: 51 (Chlorhexidine), 54 (Control)

Heterogeneity: Chi^2 = 10.84, df = 2 (P = 0.004); I^2 =82%

Test for overall effect: Z = 0.55 (P = 0.58)

Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 Chlorhexidine versus placebo/no treatment, Outcome 3 Mucositis (severe).

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

Comparison: 4 Chlorhexidine versus placebo/no treatment

Outcome: 3 Mucositis (severe)

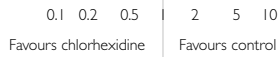
Study or subgroup	Chlorhexidine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Wahlin 1989	8/14	9/14		22.3 %	0.89 [0.49, 1.62]
Spijkervet 1989	12/15	12/15		32.2 %	1.00 [0.70, 1.43]
Foote 1994	14/25	15/27		26.7 %	1.01 [0.62, 1.64]
Sorensen 2008	9/70	21/64		18.8 %	0.39 [0.19, 0.79]
Total (95% CI)	**124**	**120**		**100.0 %**	**0.82 [0.54, 1.23]**

Total events: 43 (Chlorhexidine), 57 (Control)

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 7.44$, df = 3 (P = 0.06); $I^2 = 60\%$

Test for overall effect: Z = 0.96 (P = 0.33)

Test for subgroup differences: Not applicable

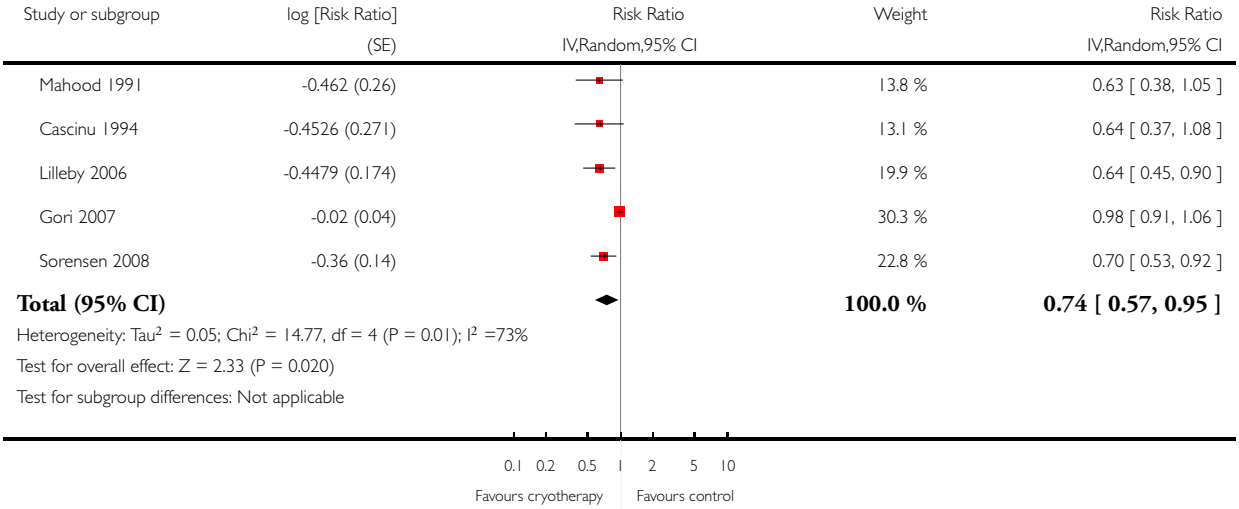


Analysis 5.1. Comparison 5 Cryotherapy versus no treatment, Outcome 1 Mucositis (any).

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

Comparison: 5 Cryotherapy versus no treatment

Outcome: 1 Mucositis (any)

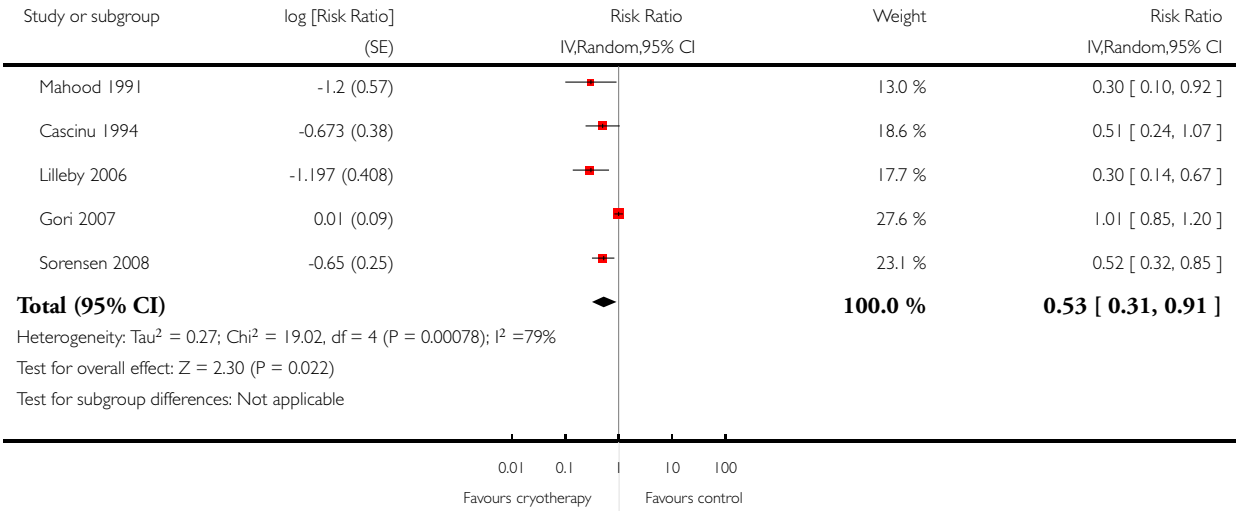


Analysis 5.2. Comparison 5 Cryotherapy versus no treatment, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 5 Cryotherapy versus no treatment

Outcome: 2 Mucositis (moderate plus severe)

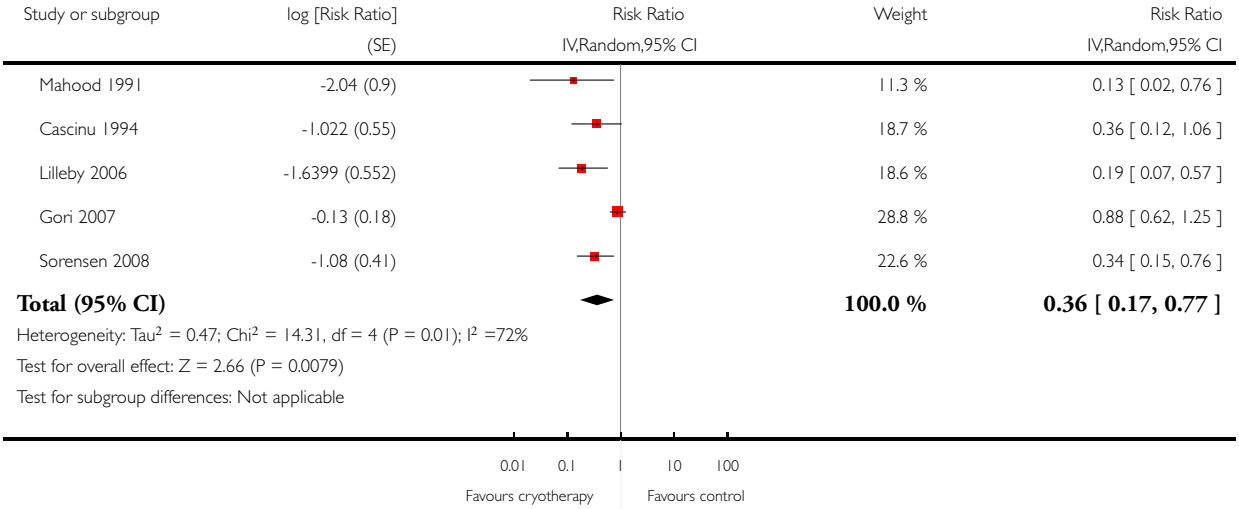


Analysis 5.3. Comparison 5 Cryotherapy versus no treatment, Outcome 3 Mucositis (severe).

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

Comparison: 5 Cryotherapy versus no treatment

Outcome: 3 Mucositis (severe)

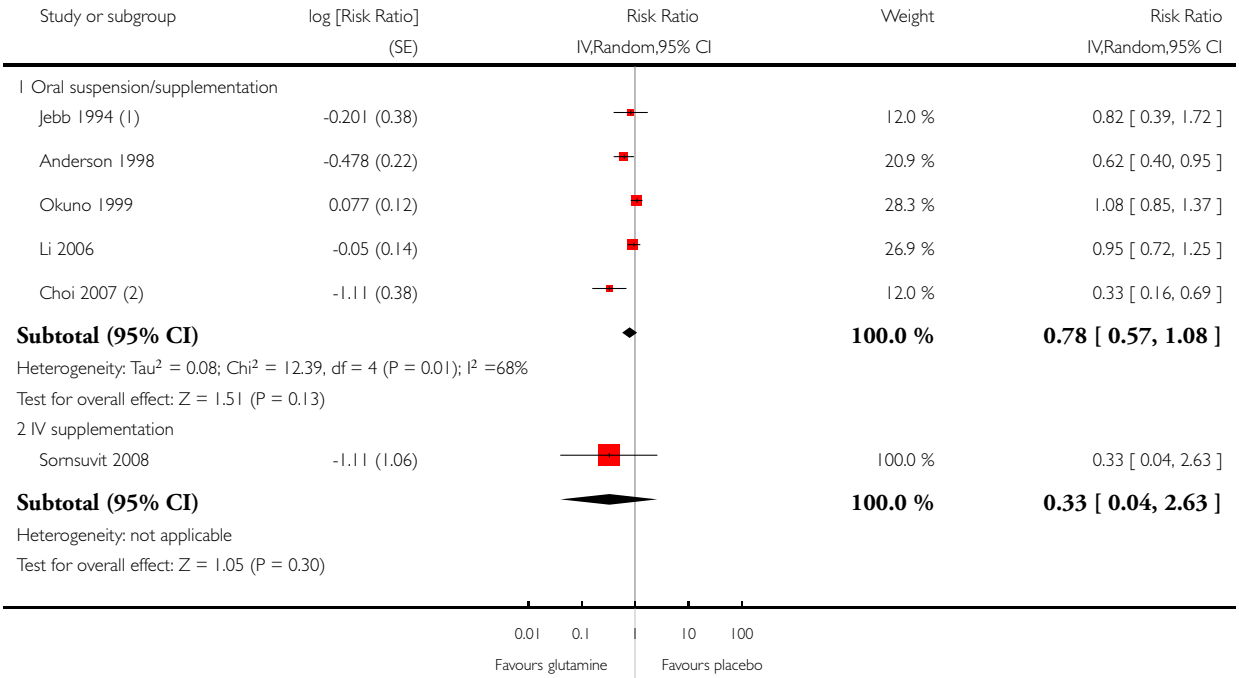


Analysis 6.1. Comparison 6 Glutamine versus placebo, Outcome 1 Mucositis (any).

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

Comparison: 6 Glutamine versus placebo

Outcome: 1 Mucositis (any)



(1) 15g/day

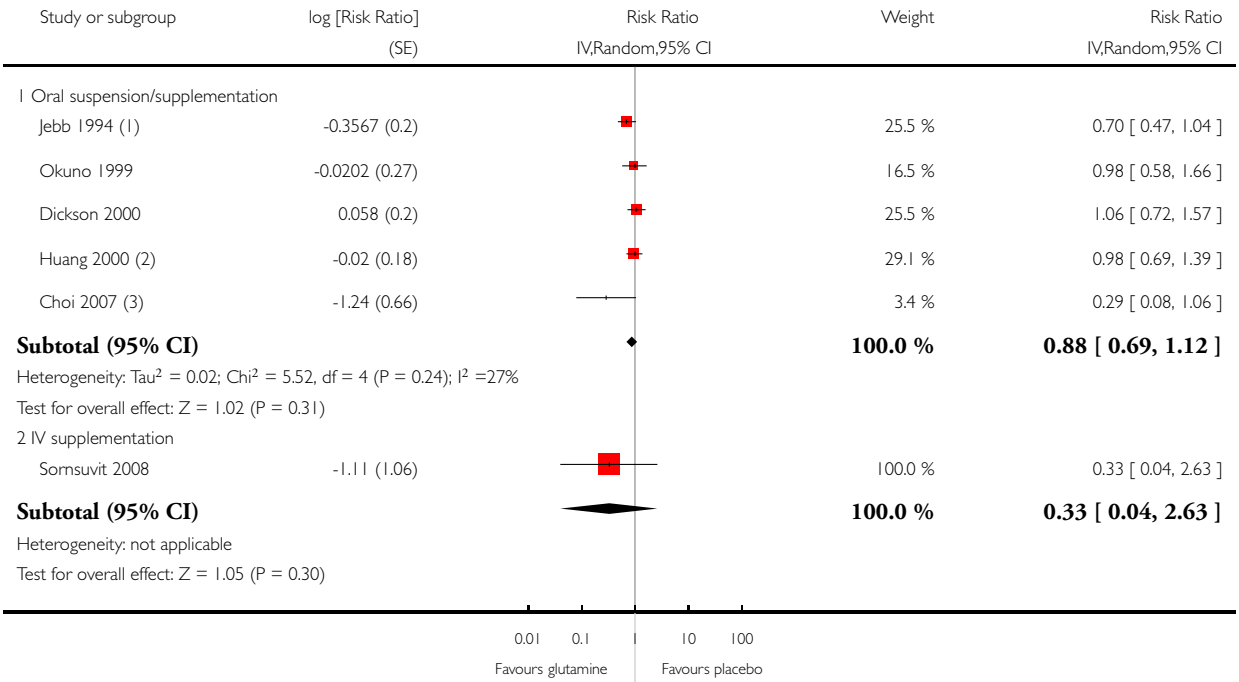
(2) control = 'best supportive care'

Analysis 6.2. Comparison 6 Glutamine versus placebo, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 6 Glutamine versus placebo

Outcome: 2 Mucositis (moderate plus severe)



(1) 15g/day

(2) swish % expectorate oral suspension

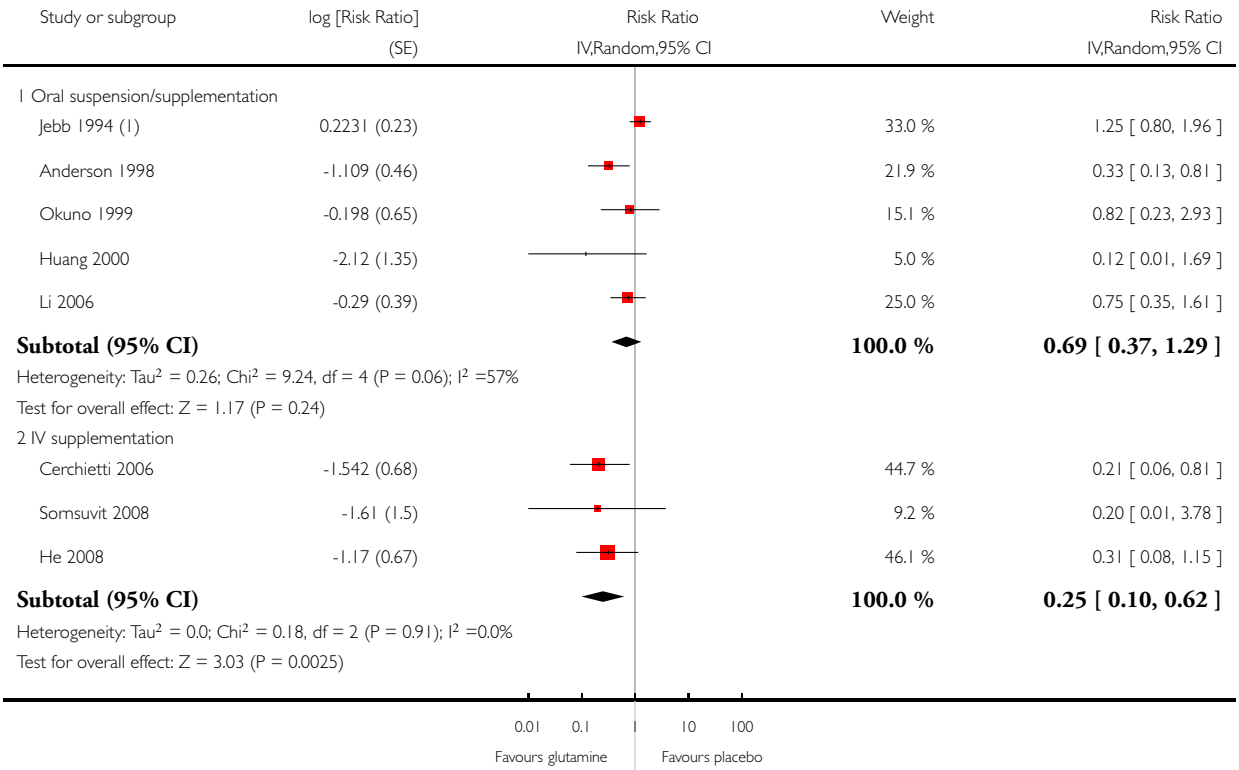
(3) control = 'best supportive care'

Analysis 6.3. Comparison 6 Glutamine versus placebo, Outcome 3 Mucositis (severe).

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

Comparison: 6 Glutamine versus placebo

Outcome: 3 Mucositis (severe)



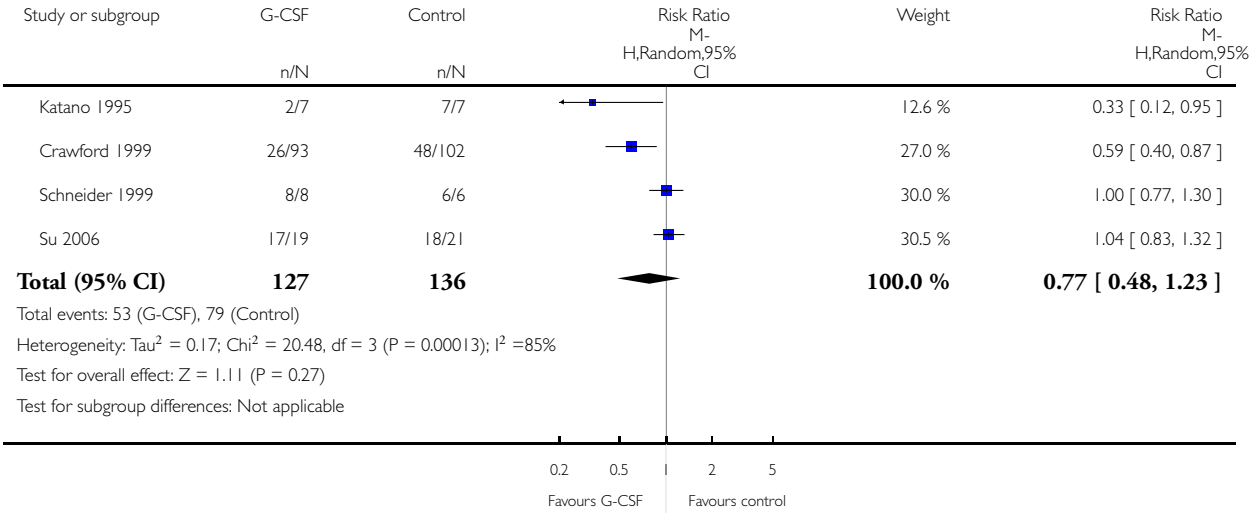
(1) 15g/day crossover design

Analysis 7.1. Comparison 7 G-CSF versus placebo or no treatment, Outcome 1 Mucositis (any).

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

Comparison: 7 G-CSF versus placebo or no treatment

Outcome: 1 Mucositis (any)

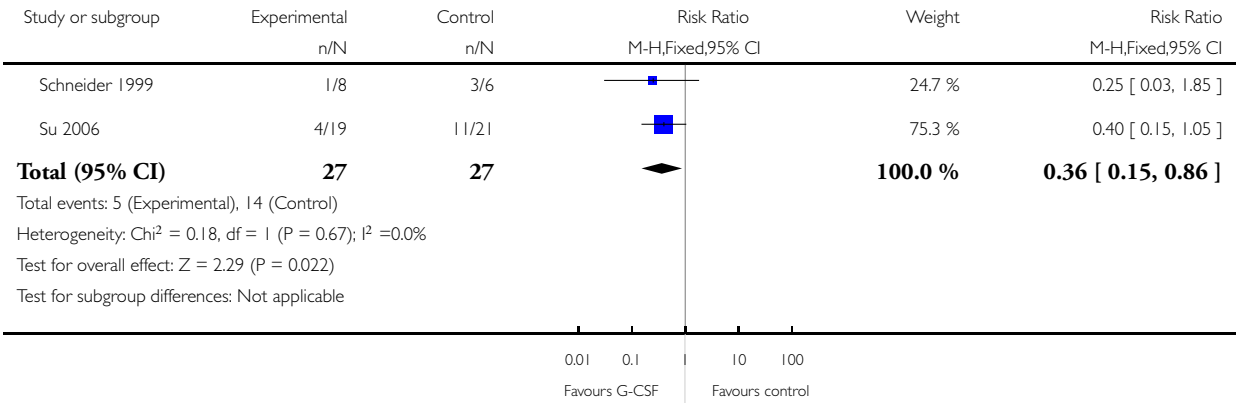


Analysis 7.2. Comparison 7 G-CSF versus placebo or no treatment, Outcome 2 Mucositis (severe).

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

Comparison: 7 G-CSF versus placebo or no treatment

Outcome: 2 Mucositis (severe)

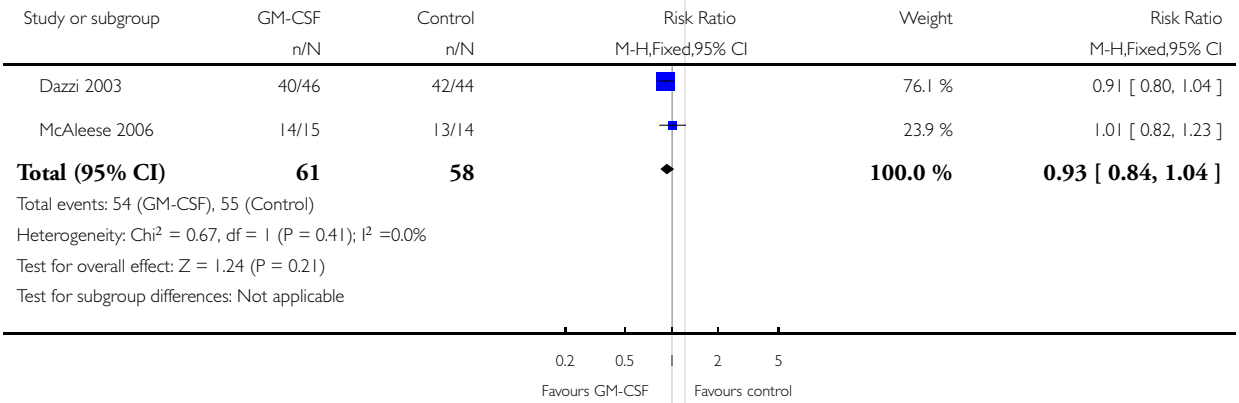


Analysis 8.1. Comparison 8 GM-CSF versus no treatment/placebo, Outcome 1 Mucositis (any).

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

Comparison: 8 GM-CSF versus no treatment/placebo

Outcome: 1 Mucositis (any)



Analysis 8.2. Comparison 8 GM-CSF versus no treatment/placebo, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 8 GM-CSF versus no treatment/placebo

Outcome: 2 Mucositis (moderate plus severe)

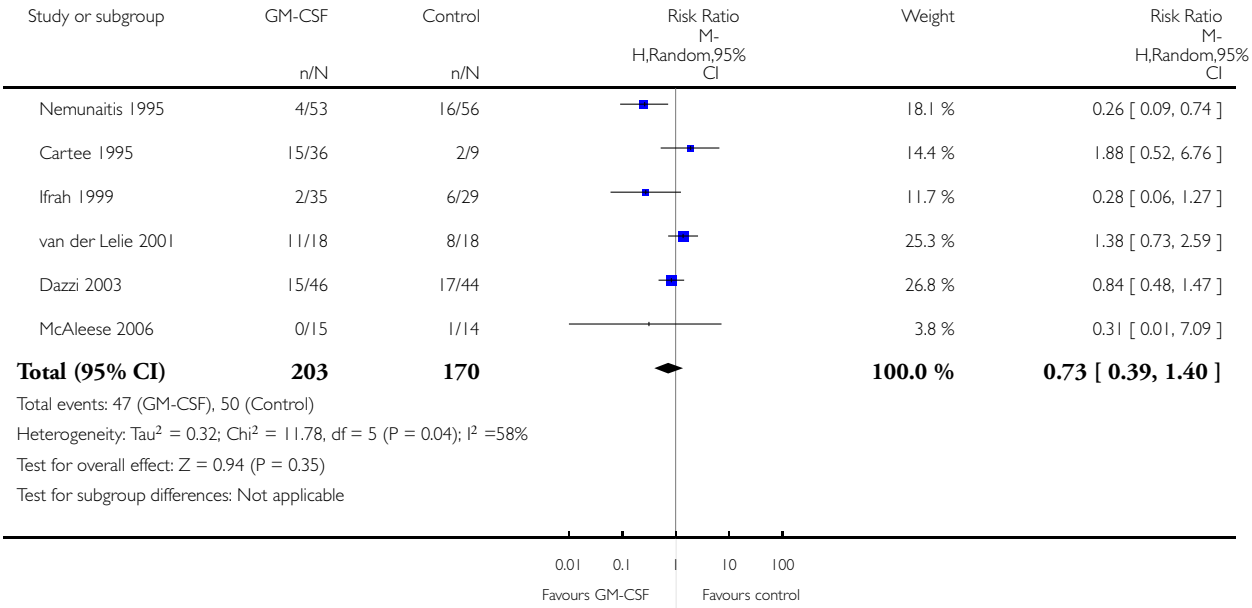
Study or subgroup	GM-CSF n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Nemunaitis 1995	42/53	47/56		77.3 %	0.94 [0.79, 1.13]
McAleese 2006	10/15	13/14		22.7 %	0.72 [0.49, 1.06]
Total (95% CI)	**68**	**70**		**100.0 %**	**0.89 [0.76, 1.05]**
Total events: 52 (GM-CSF), 60 (Control)					
Heterogeneity: Chi^2 = 1.60, df = 1 (P = 0.21); I^2 =37%					
Test for overall effect: Z = 1.37 (P = 0.17)					
Test for subgroup differences: Not applicable					

Analysis 8.3. Comparison 8 GM-CSF versus no treatment/placebo, Outcome 3 Mucositis (severe).

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

Comparison: 8 GM-CSF versus no treatment/placebo

Outcome: 3 Mucositis (severe)



Analysis 9.1. Comparison 9 Honey versus control, Outcome 1 Mucositis (any).

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

Comparison: 9 Honey versus control

Outcome: 1 Mucositis (any)

Study or subgroup	Honey n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Biswal 2003	13/20	13/20		24.1 %	1.00 [0.63, 1.58]
Rashad 2008	17/20	20/20		38.0 %	0.85 [0.70, 1.05]
Motallebnejad 2008	7/20	20/20		38.0 %	0.37 [0.21, 0.65]
Total (95% CI)	**60**	**60**		**100.0 %**	**0.70 [0.56, 0.88]**

Total events: 37 (Honey), 53 (Control)

Heterogeneity: Chi^2 = 10.71, df = 2 (P = 0.005); I^2 =81%

Test for overall effect: Z = 3.10 (P = 0.0019)

Test for subgroup differences: Not applicable

Analysis 9.2. Comparison 9 Honey versus control, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 9 Honey versus control

Outcome: 2 Mucositis (moderate plus severe)

Study or subgroup	Honey n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Biswal 2003	4/20	15/20		48.4 %	0.27 [0.11, 0.66]
Rashad 2008	11/20	16/20		51.6 %	0.69 [0.44, 1.08]
Total (95% CI)	**40**	**40**		**100.0 %**	**0.48 [0.31, 0.74]**

Total events: 15 (Honey), 31 (Control)

Heterogeneity: Chi^2 = 3.95, df = 1 (P = 0.05); I^2 =75%

Test for overall effect: Z = 3.31 (P = 0.00094)

Test for subgroup differences: Not applicable

Analysis 9.3. Comparison 9 Honey versus control, Outcome 3 Mucositis (severe).

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

Comparison: 9 Honey versus control

Outcome: 3 Mucositis (severe)

Study or subgroup	Honey n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Biswal 2003	4/20	15/20		55.6 %	0.27 [0.11, 0.66]
Rashad 2008	3/20	12/20		44.4 %	0.25 [0.08, 0.75]
Total (95% CI)	**40**	**40**		**100.0 %**	**0.26 [0.13, 0.52]**

Total events: 7 (Honey), 27 (Control)

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 3.76 (P = 0.00017)

Test for subgroup differences: Not applicable

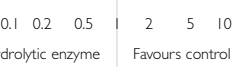
Analysis 10.1. Comparison 10 Hydrolytic enzymes versus no treatment, Outcome 1 Mucositis (any).

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

Comparison: 10 Hydrolytic enzymes versus no treatment

Outcome: 1 Mucositis (any)

Study or subgroup	Hydrolytic enz n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Kaul 1999	11/25	25/25		0.45 [0.29, 0.70]
Gujral 2001	51/53	46/46		0.96 [0.90, 1.03]



Analysis 10.2. Comparison 10 Hydrolytic enzymes versus no treatment, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 10 Hydrolytic enzymes versus no treatment

Outcome: 2 Mucositis (moderate plus severe)

Study or subgroup	Hydrolytic enz n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Kaul 1999	2/25	8/25		0.25 [0.06, 1.06]
Gujral 2001	16/53	42/46		0.33 [0.22, 0.50]
Dorr 2007	31/31	29/30		1.03 [0.94, 1.13]

Analysis 11.1. Comparison 11 Iseganan versus placebo, Outcome 1 Mucositis (moderate plus severe).

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

Comparison: 11 Iseganan versus placebo

Outcome: 1 Mucositis (moderate plus severe)

Study or subgroup	Iseganan n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Trotti 2004	230/253	156/171		54.1 %	1.00 [0.94, 1.06]
Giles 2004	143/251	158/251		45.9 %	0.91 [0.78, 1.04]
Total (95% CI)	**504**	**422**		**100.0 %**	**0.95 [0.89, 1.03]**

Total events: 373 (Iseganan), 314 (Control)

Heterogeneity: Chi^2 = 2.46, df = 1 (P = 0.12); I^2 =59%

Test for overall effect: Z = 1.26 (P = 0.21)

Test for subgroup differences: Not applicable

Analysis 11.2. Comparison 11 Iseganan versus placebo, Outcome 2 Mucositis (severe).

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

Comparison: 11 Iseganan versus placebo

Outcome: 2 Mucositis (severe)

Study or subgroup	Iseganan n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Giles 2004	138/251	153/251		55.5 %	0.90 [0.78, 1.05]
Trotti 2004	167/253	103/171		44.5 %	1.10 [0.94, 1.27]
Total (95% CI)	**504**	**422**		**100.0 %**	**0.99 [0.89, 1.10]**

Total events: 305 (Iseganan), 256 (Control)

Heterogeneity: Chi^2 = 3.25, df = 1 (P = 0.07); I^2 =69%

Test for overall effect: Z = 0.22 (P = 0.83)

Test for subgroup differences: Not applicable

Analysis 12.1. Comparison 12 Keratinocyte GF versus placebo, Outcome 1 Mucositis (any).

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

Comparison: 12 Keratinocyte GF versus placebo

Outcome: 1 Mucositis (any)

Study or subgroup	KGF n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Blazar 2006	60/65	31/31		61.8 %	0.93 [0.86, 1.01]
Rosen 2006	15/28	30/36		38.2 %	0.64 [0.44, 0.93]
Total (95% CI)	**93**	**67**		**100.0 %**	**0.82 [0.71, 0.94]**

Total events: 75 (KGF), 61 (Control)

Heterogeneity: Chi^2 = 10.11, df = 1 (P = 0.001); I^2 =90%

Test for overall effect: Z = 2.79 (P = 0.0052)

Test for subgroup differences: Not applicable

Analysis 12.2. Comparison 12 Keratinocyte GF versus placebo, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 12 Keratinocyte GF versus placebo

Outcome: 2 Mucositis (moderate plus severe)

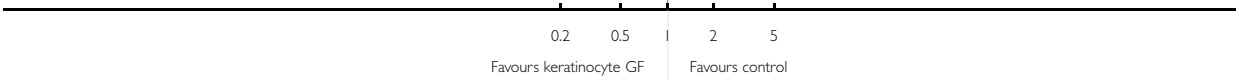
Study or subgroup	KGF n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Meropol 2003	23/54	18/27		10.5 %	0.64 [0.42, 0.96]
Freytes 2004	16/28	14/14		12.8 %	0.59 [0.42, 0.82]
Spielberger 2004	98/106	106/106		21.3 %	0.92 [0.87, 0.98]
Blazar 2006	53/65	31/31		19.7 %	0.82 [0.73, 0.93]
Rosen 2006	8/28	22/36		6.0 %	0.47 [0.25, 0.89]
Brizel 2008	60/65	31/32		20.6 %	0.95 [0.87, 1.05]
Vadhan-Raj 2010	13/32	14/16		9.2 %	0.46 [0.29, 0.73]
Total (95% CI)	**378**	**262**		**100.0 %**	**0.74 [0.62, 0.89]**

Total events: 271 (KGF), 236 (Control)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 50.75$, df = 6 (P<0.00001); $I^2 = 88\%$

Test for overall effect: Z = 3.15 (P = 0.0016)

Test for subgroup differences: Not applicable



Analysis 12.3. Comparison 12 Keratinocyte GF versus placebo, Outcome 3 Mucositis (severe).

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

Comparison: 12 Keratinocyte GF versus placebo

Outcome: 3 Mucositis (severe)

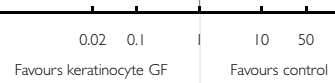
Study or subgroup	KGF n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Freytes 2004	4/28	1/14		1.1 %	2.00 [0.25, 16.26]
Spielberger 2004	67/106	104/106		36.8 %	0.64 [0.56, 0.75]
Blazar 2006	43/65	24/31		27.7 %	0.85 [0.66, 1.11]
Rosen 2006	1/28	4/36		1.1 %	0.32 [0.04, 2.72]
Brizel 2008	43/65	26/32		29.1 %	0.81 [0.64, 1.04]
Vadhan-Raj 2010	4/32	8/16		4.2 %	0.25 [0.09, 0.71]
Total (95% CI)	**324**	**235**		**100.0 %**	**0.72 [0.58, 0.90]**

Total events: 162 (KGF), 167 (Control)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.37$, df = 5 (P = 0.07); $I^2 = 52\%$

Test for overall effect: Z = 2.86 (P = 0.0042)

Test for subgroup differences: Not applicable

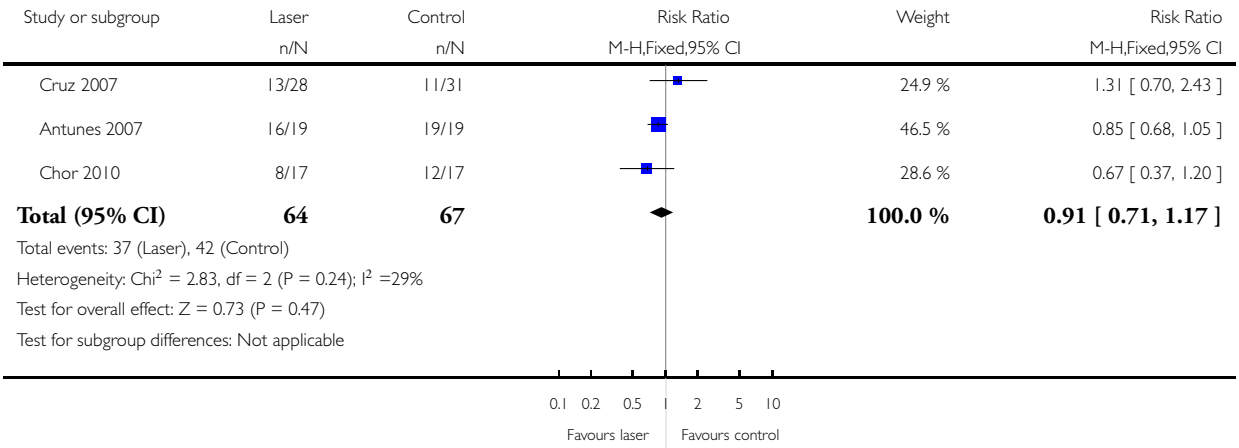


Analysis 13.1. Comparison 13 Laser versus no treatment, Outcome 1 Mucositis (any).

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

Comparison: 13 Laser versus no treatment

Outcome: 1 Mucositis (any)

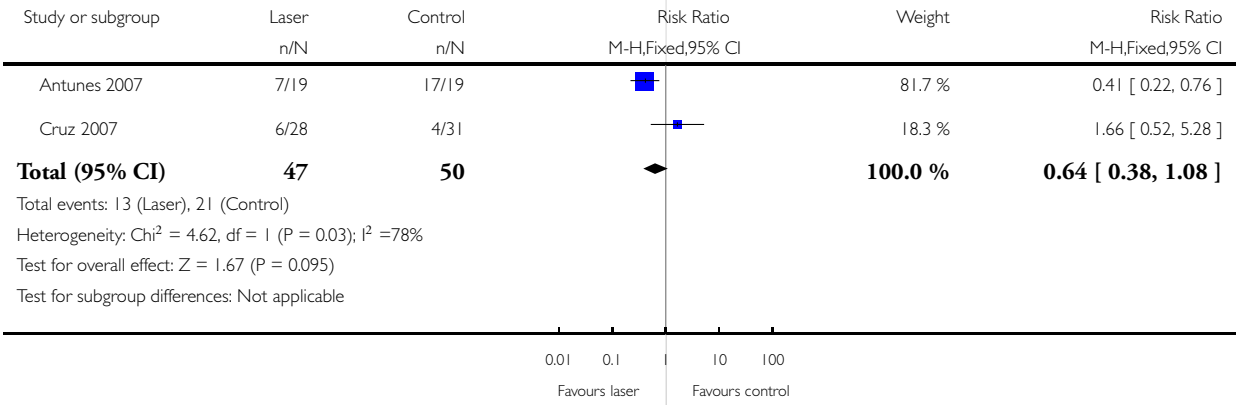


Analysis 13.2. Comparison 13 Laser versus no treatment, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 13 Laser versus no treatment

Outcome: 2 Mucositis (moderate plus severe)



Analysis 13.3. Comparison 13 Laser versus no treatment, Outcome 3 Mucositis (severe).

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

Comparison: 13 Laser versus no treatment

Outcome: 3 Mucositis (severe)

Study or subgroup	Laser n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Antunes 2007	1/19	13/19		82.0 %	0.08 [0.01, 0.53]
Cruz 2007	2/28	3/31		18.0 %	0.74 [0.13, 4.10]
Total (95% CI)	**47**	**50**		**100.0 %**	**0.20 [0.06, 0.62]**

Total events: 3 (Laser), 16 (Control)

Heterogeneity: $Chi^2 = 3.20$, df = 1 (P = 0.07); $I^2 = 69\%$

Test for overall effect: Z = 2.76 (P = 0.0058)

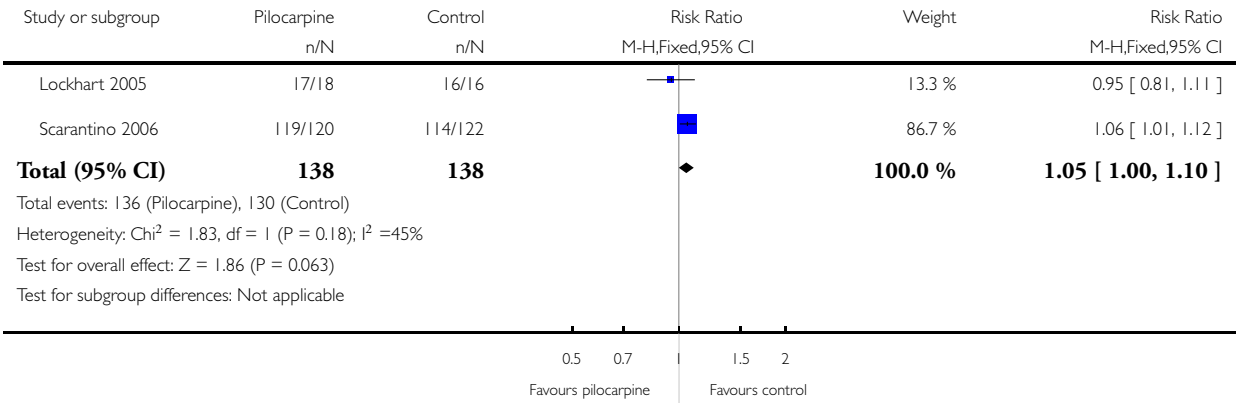
Test for subgroup differences: Not applicable

Analysis 14.1. Comparison 14 Pilocarpine versus placebo, Outcome 1 Mucositis (any).

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

Comparison: 14 Pilocarpine versus placebo

Outcome: 1 Mucositis (any)

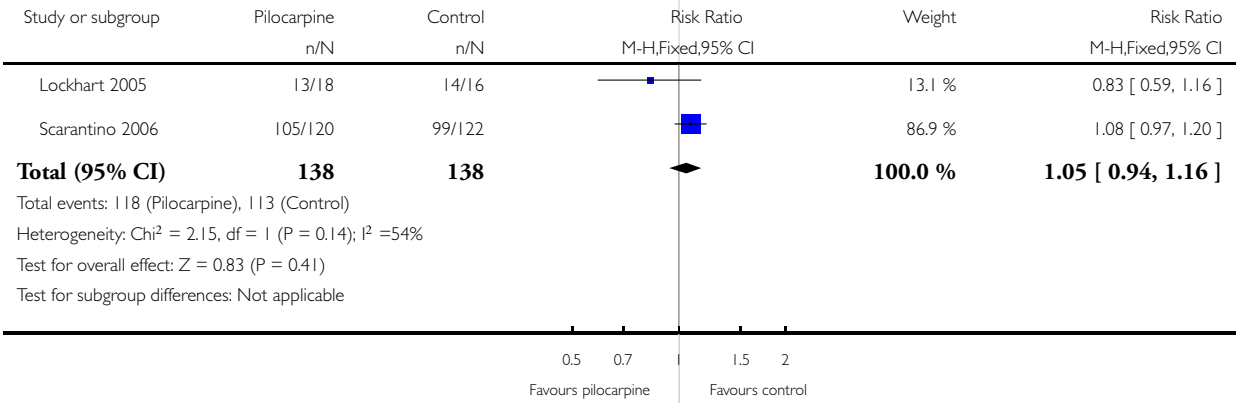


Analysis 14.2. Comparison 14 Pilocarpine versus placebo, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 14 Pilocarpine versus placebo

Outcome: 2 Mucositis (moderate plus severe)

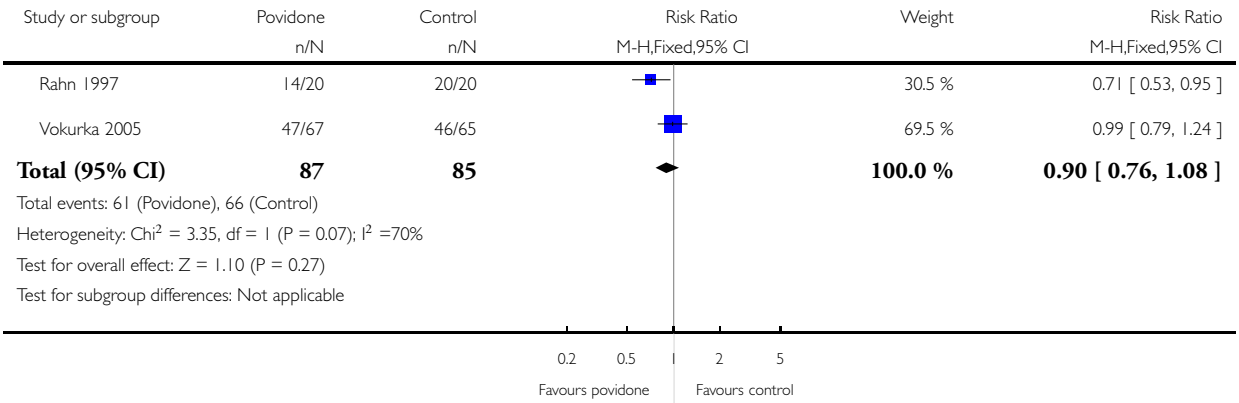


Analysis 15.1. Comparison 15 Povidone versus water, Outcome 1 Mucositis (any).

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

Comparison: 15 Povidone versus water

Outcome: 1 Mucositis (any)

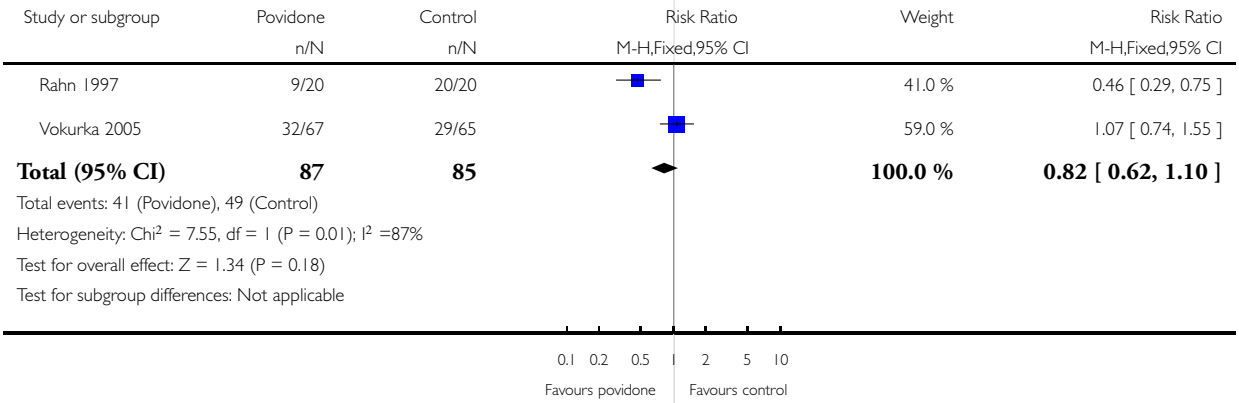


Analysis 15.2. Comparison 15 Povidone versus water, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 15 Povidone versus water

Outcome: 2 Mucositis (moderate plus severe)



Analysis 15.3. Comparison 15 Povidone versus water, Outcome 3 Mucositis (severe).

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

Comparison: 15 Povidone versus water

Outcome: 3 Mucositis (severe)

Study or subgroup	Povidone n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rahn 1997	4/20	13/20		43.0 %	0.31 [0.12, 0.78]
Vokurka 2005	16/67	17/65		57.0 %	0.91 [0.51, 1.65]
Total (95% CI)	**87**	**85**		**100.0 %**	**0.65 [0.40, 1.06]**

Total events: 20 (Povidone), 30 (Control)

Heterogeneity: Chi^2 = 3.73, df = 1 (P = 0.05); I^2 =73%

Test for overall effect: Z = 1.72 (P = 0.085)

Test for subgroup differences: Not applicable

Analysis 16.1. Comparison 16 Prostaglandin versus placebo, Outcome 1 Mucositis (any).

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

Comparison: 16 Prostaglandin versus placebo

Outcome: 1 Mucositis (any)

Study or subgroup	Prostaglandin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Labar 1993	29/31	29/29		40.8 %	0.94 [0.84, 1.05]
Duenas 1996	8/9	2/7		3.0 %	3.11 [0.94, 10.27]
Veness 2006	41/42	41/41		56.2 %	0.98 [0.91, 1.04]
Total (95% CI)	**82**	**77**		**100.0 %**	**1.03 [0.94, 1.12]**

Total events: 78 (Prostaglandin), 72 (Control)

Heterogeneity: Chi^2 = 7.87, df = 2 (P = 0.02); I^2 =75%

Test for overall effect: Z = 0.58 (P = 0.57)

Test for subgroup differences: Not applicable

Analysis 16.2. Comparison 16 Prostaglandin versus placebo, Outcome 2 Mucositis (severe).

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

Comparison: 16 Prostaglandin versus placebo

Outcome: 2 Mucositis (severe)

Study or subgroup	Prostaglandin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Labar 1993	17/31	15/29		46.0 %	1.06 [0.66, 1.70]
Veness 2006	18/42	18/41		54.0 %	0.98 [0.60, 1.60]
Total (95% CI)	**73**	**70**		**100.0 %**	**1.01 [0.72, 1.43]**

Total events: 35 (Prostaglandin), 33 (Control)

Heterogeneity: $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 0.08 (P = 0.93)

Test for subgroup differences: Not applicable

Analysis 17.1. Comparison 17 PTA antibiotic pastille or paste versus placebo/no treatment, Outcome 1 Mucositis (any).

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

Comparison: 17 PTA antibiotic pastille or paste versus placebo/no treatment

Outcome: 1 Mucositis (any)

Study or subgroup	PTA antibiotic n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Symonds 1996	85/112	97/109		74.1 %	0.85 [0.75, 0.96]
Wijers 2001	32/39	34/38		25.9 %	0.92 [0.76, 1.10]
Total (95% CI)	**151**	**147**		**100.0 %**	**0.87 [0.78, 0.96]**

Total events: 117 (PTA antibiotic), 131 (Control)

Heterogeneity: $Chi^2 = 0.42$, df = 1 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 2.67 (P = 0.0077)

Test for subgroup differences: Not applicable

Analysis 17.2. Comparison 17 PTA antibiotic pastille or paste versus placebo/no treatment, Outcome 2 Mucositis (severe).

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

Comparison: 17 PTA antibiotic pastille or paste versus placebo/no treatment

Outcome: 2 Mucositis (severe)

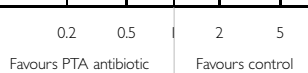
Study or subgroup	PTA antibiotic n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wijers 2001	15/39	18/38		41.2 %	0.81 [0.48, 1.37]
Stokman 2003	22/28	27/30		58.8 %	0.87 [0.70, 1.10]
Total (95% CI)	**67**	**68**		**100.0 %**	**0.85 [0.66, 1.09]**

Total events: 37 (PTA antibiotic), 45 (Control)

Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable



Analysis 18.1. Comparison 18 Radiotherapy: am versus pm, Outcome 1 Mucositis (severe).

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

Comparison: 18 Radiotherapy: am versus pm

Outcome: 1 Mucositis (severe)

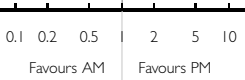
Study or subgroup	AM n/N	PM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bjarnason 2009	63/101	55/104		82.0 %	1.18 [0.93, 1.49]
Goyal 2009	7/88	12/89		18.0 %	0.59 [0.24, 1.43]
Total (95% CI)	**189**	**193**		**100.0 %**	**1.07 [0.85, 1.36]**

Total events: 70 (AM), 67 (PM)

Heterogeneity: $Chi^2 = 2.37$, df = 1 (P = 0.12); I^2 =58%

Test for overall effect: Z = 0.59 (P = 0.56)

Test for subgroup differences: Not applicable



Analysis 19.1. Comparison 19 Sucralfate versus placebo/usual care, Outcome 1 Mucositis (any).

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

Comparison: 19 Sucralfate versus placebo/usual care

Outcome: 1 Mucositis (any)

Study or subgroup	Sucralfate n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Makkonen 1994	20/20	19/20		20.3 %	1.05 [0.92, 1.20]
Castagna 2001	43/51	45/51		46.7 %	0.96 [0.82, 1.12]
Nottage 2003	32/41	31/39		33.0 %	0.98 [0.78, 1.23]
Total (95% CI)	**112**	**110**		**100.0 %**	**0.98 [0.88, 1.10]**

Total events: 95 (Sucralfate), 95 (Control)

Heterogeneity: $Chi^2 = 1.05$, df = 2 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 0.30 (P = 0.76)

Test for subgroup differences: Not applicable

Analysis 19.2. Comparison 19 Sucralfate versus placebo/usual care, Outcome 2 Mucositis (moderate plus severe).

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

Comparison: 19 Sucralfate versus placebo/usual care

Outcome: 2 Mucositis (moderate plus severe)

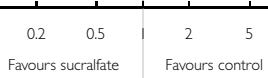
Study or subgroup	Sucralfate n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Shenep 1988	17/24	18/24		32.1 %	0.94 [0.67, 1.33]
Makkonen 1994	14/20	15/20		29.7 %	0.93 [0.64, 1.37]
Franzen 1995	7/24	15/24		15.3 %	0.47 [0.23, 0.94]
Cengiz 1999	9/18	9/10		22.8 %	0.56 [0.33, 0.92]
Total (95% CI)	**86**	**78**		**100.0 %**	**0.75 [0.54, 1.04]**

Total events: 47 (Sucralfate), 57 (Control)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.16$, df = 3 (P = 0.10); $I^2 = 51\%$

Test for overall effect: Z = 1.73 (P = 0.083)

Test for subgroup differences: Not applicable

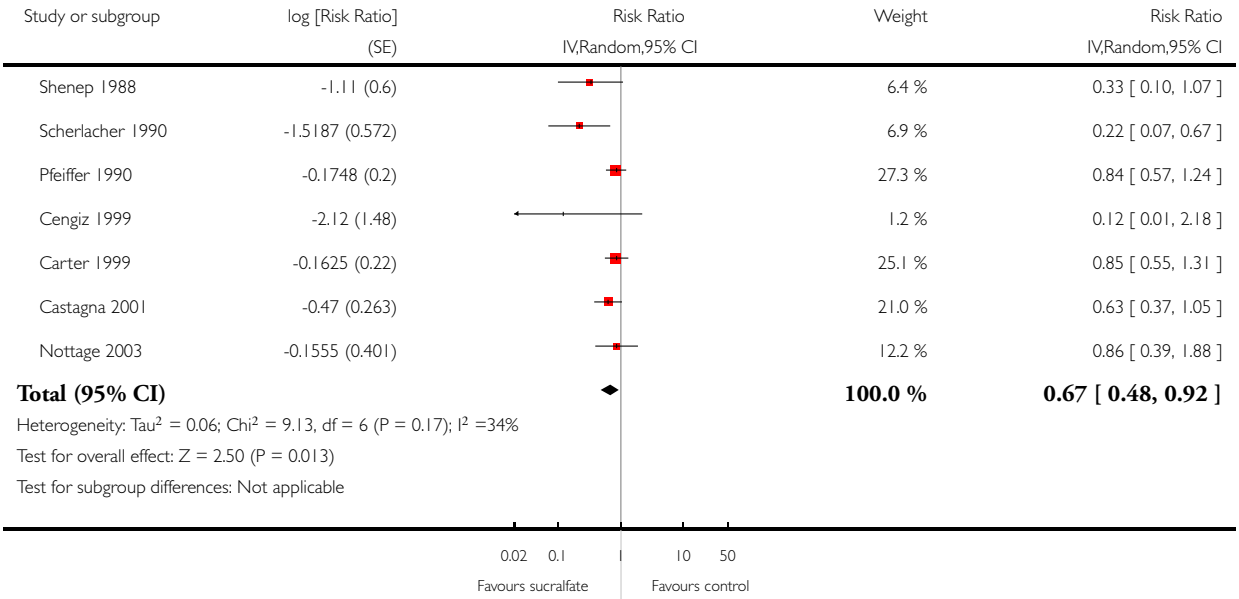


Analysis 19.3. Comparison 19 Sucralfate versus placebo/usual care, Outcome 3 Mucositis (severe).

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

Comparison: 19 Sucralfate versus placebo/usual care

Outcome: 3 Mucositis (severe)



ADDITIONAL TABLES

Table 1. Outcome categories where only one study provided data - active versus placebo/no treatment

		Experimental		Control		RR (95%CI)	P value
	Mucositis category	Events/ Mean (SD)	Total	Events/ Mean (SD)	Total		
Aciclovir versus placebo Bubley 1989	Any	18	27	15	30	1.33 (0.85, 2.08)	0.21
Aloe vera versus placebo	Any Puataweepong 2009	29	30	31	31	0.97 (0.88, 1.06)	0.46
	Severe Su 2004	1	30	8	31	0.13 (0.02, 0.97)	0.05

Table 1. Outcome categories where only one study provided data - active versus placebo/no treatment (*Continued*)

BCoG antibiotic pastilles El Sayed 2002	Any	62	69	60	68	1.02 (0.91, 1.15)	0.76
	Moderate plus severe	50	69	53	68	0.93 (0.77, 1.13)	0.46
	Severe	31	69	34	68	0.90 (0.63, 1.28)	0.55
Benzydamine versus placebo	Any Prada 1987	12	19	16	17	0.67 (0.47, 0.97)	0.03
	Severe Kazemian 2009	17	39	33	42	0.55 (0.38, 0.82)	0.003
Beta carotene versus no treatment control	Severe Mills 1988	3	10	8	10	0.38 (0.14, 1.02)	0.05
Camomile versus placebo Fidler 1996	Any	33	82	37	82	0.89 (0.62, 1.27)	0.53
	Moderate plus severe	12	82	19	82	0.63 (0.33, 1.22)	0.17
	Severe	8	82	7	82	1.14 (0.43, 3.01)	0.79
Chewing gum versus no chewing gum Gandemer 2007	Any	48	70	55	70	0.87 (0.71, 1.07)	0.18
	Severe	36	70	31	70	1.16 (0.82, 1.64)	0.40
Clarithromycin (systemic antibiotic) versus no treatment Yuen 2001	Moderate plus severe	18	35	26	35	0.69 (0.48, 1.01)	0.06
Dental stent versus no treatment control Qin 2007	Moderate plus severe	14	19	21	24	0.84 (0.62, 1.15)	0.27

Table 1. Outcome categories where only one study provided data - active versus placebo/no treatment (*Continued*)

	Severe	5	19	9	24	0.70 (0.28, 1.75)	0.45
Epidermal growth factor versus placebo Wu 2009	Moderate plus severe	32	76	17	27	0.67 (0.45, 0.99)	0.04
G-CSF versus placebo Su 2006	Moderate plus severe	11	19	15	21	0.81 (0.51, 1.30)	0.38
Histamine gel versus placebo Elad 2006	Any	17	20	12	19	1.35 (0.91, 1.99)	0.14
	Severe	2	20	2	19	0.95 (0.15, 6.08)	0.96
Hydrolytic enzymes (papain, trypsin, chymotrypsin, pancreatin, bromelain) versus no treatment Kaul 1999	Severe	0	25	2	25	0.20 (0.01, 3.97)	0.29
Indomethacin versus placebo Pillsbury 1986	Moderate plus severe	10	10	8	8	1.00 (0.82, 1.23)	1.00
Indigo wood root versus saline (placebo) You 2009	Moderate to severe	8	11	9	9	0.75 (0.50, 1.10)	0.14
	Severe	1	11	6	9	0.14 (0.02, 0.93)	0.04
Intestinal trefoil factor versus placebo Peterson 2009	Any	23	66	22	33	0.52 (0.35, 0.79)	0.002

Table 1. Outcome categories where only one study provided data - active versus placebo/no treatment (*Continued*)

	Moderate plus severe	7	66	16	33	0.22 (0.10, 0.48)	0.0001
	Severe	1	66	0	33	1.52 (0.06, 36.39)	0.80
Oral care protocol versus none	Any Shieh 1997	12	20	10	10	0.62 (0.43, 0.91)	0.01
	Moderate plus severe Borowski 1994	64	75	70	75	0.91 (0.82, 1.02)	0.12
	Severe Borowski 1994	49	75	58	75	0.84 (0.69, 1.04)	0.11
Pentoxifylline versus no treatment Attal 1993	Moderate plus severe	30	70	30	70	1.00 (0.68, 1.47)	1.00
Pilocarpine versus placebo Lockhart 2005	Severe	12	18	12	16	0.89 (0.58, 1.37)	0.59
Prednisone versus placebo Leborgne 1997	Any	28	32	29	34	1.03 (0.85, 1.24)	0.79
	Moderate plus severe	16	32	24	34	0.71 (0.47, 1.07)	0.10
	Severe	3	32	5	34	0.64 (0.17, 2.45)	0.51
Prostaglandin versus placebo (Veness 2006)	Moderate plus severe	36	42	37	41	0.95 (0.81, 1.11)	0.53
Propantheline versus placebo Ahmed 1993	Any	2	6	5	6	0.40 (0.12, 1.31)	0.13

Table 1. Outcome categories where only one study provided data - active versus placebo/no treatment (*Continued*)

PTA antibiotic paste (Wijers 2001)	Moderate plus severe	26	39	28	38	0.90 (0.68, 1.21)	0.5
Shenqifanghou versus no treatment Hu 2005	Any	60	70	67	70	0.90 (0.80, 1.00)	0.04
	Moderate plus severe	30	70	59	70	0.51 (0.38, 0.68)	0.00001
	Severe	10	70	50	70	0.20 (0.11, 0.36)	0.00001
Superoxide dismutase versus placebo Tu 1998	Any	59	119	17	40	1.17 (0.78, 1.75)	0.45
Sucralfate mouthwash plus gel on skin versus placebo mouthwash plus gel on skin (Evensen 2001)	Any	30	30	28	30	1.07 (0.96, 1.20)	0.24
	Moderate plus severe	29	30	24	30	1.21 (1.00, 1.46)	0.05
	Severe	26	30	23	30	1.13 (0.89, 1.44)	0.32
Traumeel versus placebo Oberbaum 2001	Any	10	15	14	15	0.71 (0.49, 1.05)	0.08
Zinc sulphate versus placebo Ertekin 2004	Any	13	15	12	12	0.88 (0.69, 1.11)	0.28
	Moderate plus severe	5	15	12	12	0.36 (0.18, 0.71)	0.003
	Severe	0	15	8	12	0.05 (0.00, 0.75)	0.03

CI = confidence interval; RR = risk ratio; SD = standard deviation.

Table 2. Text only inclusions

Intervention	Study	Text
Amifostine versus no treatment	Vacha 2003	CTC mucositis index used. Results presented as weekly means for both arms with standard deviations. Text indicated statistically significant difference in favour of amifostine at 2 weeks but does not mention overall result
Benzydamine versus placebo	Epstein 1989	Signs of mucositis were recorded by area of involvement, severity of inflammation, severity of ulceration and maximum size of ulceration for each region of the oral cavity. Results in Table 3 indicate borderline statistically significant differences in favour of benzydamine. Maximum size of ulcerations (P = 0.04); total area of ulcerations (P = 0.05); average area of mucositis (P = 0.050)
Benzydamine versus placebo	Epstein 2001	Area under the curve of mean mucositis cores presented for different radiotherapy intervals. Overall there was a statistically significant difference in favour of benzydamine (P = 0.006), Table 4
Chlorhexidine versus placebo	McGaw 1985	Hickey (0-3 scale) index for mucositis used over 4-week period. During the third and fourth weeks the average mucositis scores were significantly higher in the control group
Chlorhexidine versus povidone-iodine, salt/soda versus water	Madan 2008	After 4 weeks there was a statistically significant decrease in mean mucositis scores in each of the active treatment groups compared to placebo
Cryotherapy versus no treatment control	Svanberg 2007	"The results demonstrated that oral cryotherapy alleviated the development of mucositis and oral pain, which resulted in a reduction in the number of days of iv opioids for patients treated with autologous BMT."
GM-CSF versus no treatment control	Chi 1995	Cross-over study showing period effect but indicating GM-CSF significantly prevents mucositis (P < 0.001)
Laser versus placebo light treatment	Bensadoun 1999	Parallel group study mucositis measured on 0-4 scale. Mean calculated for each patient over 7 weeks. Quote "the mean grade of mucositis during radiotherapy was 2.1 +/ 0.26 for the group without laser and 1.7 +/- 0.26 for the group with laser (P = 0.01)."
Laser versus sham laser treatment	Schubert 2007	OMI appropriate index (Schubert 1992). Quote: "Figure 1 shows the mean OMI over time by treatment group. The placebo patient scores are higher on average than the laser patient scores at nearly every time point, signifying more severe mucositis over the course of the study.." The authors then present day 11 data and statistical test for that day (P = 0.06) "The peak severity of mucositis that generally occurs during the second week of transplant was reduced in the 650 nm laser group." The results of the overall burden over time in Table 2 showed the

Table 2. Text only inclusions (*Continued*)

		differences in the unadjusted model to be non-significant. Only one difference comparing low-level laser with placebo was significant in the adjusted model (P = 0.03)
Prostaglandin versus placebo	Hanson 1995	Data from 2 centres reported separately. Overall ANOVA for 1 centre showed no significant difference. The other centre found statistically significant differences for weeks 4 and 5 with less mucositis in the intervention group (P < 0.05)
Sucralfate versus placebo	Epstein 1994	Signs of mucositis were recorded by area of involvement, severity of inflammation, severity of ulceration and maximum size of ulceration for each region of the oral cavity. No statistically significant difference was seen in mucositis ulceration or the composite mucositis score (Table 3). Total mucositis score: Placebo (n = 17) mean = 18.7 +/- 21.3 Sucralfate (n = 16) mean = 22.3 +/- 31.2 Total mucosal ulceration: Placebo (n = 17) mean = 15.3 +/- 17.6 Sucralfate (n = 16) mean = 19.4 +/- 19.8.
Sucralfate versus placebo	Lievens 1998	Mucositis scores on 0-6 ECOG scale. Graph (fig 1) displays mean mucositis scores for each week 1-7. Quote: "Comparing the time course of the mean scores for . . .mucositis . . . no statistically significant differences between the two treatment arms were observed." Quote: "At 5 week when the mucosal reaction tends to be most severe a clear but not statistically significant advantage is seen for sucralfate as opposed to placebo."
Zinc versus placebo	Lin 2006	RTOG mucositis index used. Results presented as graphs. Quote: "This study no significant difference was found in the improvement of radiation mucositis and dermatitis during the 2 weeks between the patients with zinc supplement and those without."

ANOVA = analysis of variance; BMT = bone marrow transplant; CTC = Common Toxicity Criteria; ECOG = Eastern Cooperative Oncology Group; GM-CSF = granulocyte/macrophage colony-stimulating factor; OMI = oral mucositis index; RTOG = Radiation Therapy Oncology Group.

Table 3. Outcome categories where only one study provided data - two active interventions

		Experimental		RR (95%CI)		RR (95%CI)	P value
	Mucositis category	**Events/ Mean (SD)**	**Total**	**Events/ Mean (SD)**	**Total**		
Chinese herbs (coastal glenhnia,	Moderate	23	52	47	49	0.46 (0.34, 0.63)	0.00001

Table 3. Outcome categories where only one study provided data - two active interventions (*Continued*)

dwarf lilyturf tuber root, rehmannia dried root, figwort root, spreading hedyotis herb, belamcaude rhizome, platycodom root, shinyleaf pricklyoash root, honeysuckle flower, licorice root, lalang grass rhizome) versus Dobell's solution Huang 2003	Severe	5	52	30	49	0.16 (0.07, 0.37)	0.0001
Chinese herbs (cork-tree bark, Chinese gall, European vebena herb, catechu, weeping forsythia fruit and burneol) versus Dobell's solution Wang 2002	Any	8	76	17	71	0.44 (0.20, 0.95)	0.04
	Moderate plus severe	4	76	14	71	0.27 (0.09, 0.77)	0.01
	Severe	0	76	5	71	0.09 (0.00, 1.51)	0.09
Chlorhexidine versus cryotherapy Sorensen 2008	Any	39	70	34	63	1.03 (0.76, 1.41)	0.84
	Moderate plus severe	20	70	16	63	1.13 (0.64, 1.97)	0.68
	Severe	9	70	7	63	1.16 (0.46, 2.92)	0.76
Cryotherapy 30 versus 60 minutes Rocke 1993	Any	33	89	37	89	0.89 (0.62, 1.29)	0.54

Table 3. Outcome categories where only one study provided data - two active interventions (*Continued*)

	Moderate plus severe	13	89	19	89	0.68 (0.36, 1.30)	0.25
	Severe	6	89	10	89	0.60 (0.23, 1.58)	0.30
GM-CSF versus sucralfate Saarilahti 2002	Moderate plus severe	19	21	18	19	0.96 (0.80, 1.14)	0.61
	Severe	6	21	10	19	0.54 (0.24, 1.21)	0.13
Keratinocyte 50 versus 25 mg Freytes 2004	Moderate plus severe	7	14	9	14	0.78 (0.40, 1.49)	0.45
	Severe	1	14	3	14	0.33 (0.04, 2.83)	0.31
Laser versus povidone Arun Maiya 2006	Moderate plus severe	7	25	25	25	0.29 (0.16, 0.54)	< 0.0001
	Severe	0	25	25	25	0.02 (0.00, 0.31)	0.005
Polaprezinc versus azulene oral rinse Watanabe 2010	Any	13	16	15	15	0.82 (0.63, 1.06)	0.13
	Moderate plus severe	6	16	13	15	0.43 (0.22, 0.84)	0.01
	Severe	1	16	10	15	0.09 (0.01, 0.65)	0.02
Radiotherapy morning versus afternoon Goyal 2009	Moderate plus severe	29	88	42	89	0.70 (0.48, 1.01)	0.06
Yangyin humo decoctalion versus 'traditional Western medicine' (lidocaine (iv), dexamethasone, gentamycin, vita-	Moderate	11	21	17	21	0.65 (0.41, 1.02)	0.06

Table 3. Outcome categories where only one study provided data - two active interventions (*Continued*)

min B12, bicarbonate) Dai 2009	Severe	4	21	7	21	0.57 (0.20, 1.66)	0.30

CI = confidence interval; RR = risk ratio; SD = standard deviation.

APPENDICES

Appendix 1. Cochrane Oral Health Group Trials Register search strategy

((neoplasm* OR leukemia OR leukaemia OR leukaemia OR lymphoma* OR plasmacytoma OR "histiocytosis malignant" OR reticuloendotheliosis OR "sarcoma mast cell" OR "Letterer Siwe disease" OR "immunoproliferative small intestine disease" OR "Hodgkin disease" OR "histiocytosis malignant" OR "bone marrow transplant*" OR cancer* Or tumor* OR tumour* OR malignan* OR neutropeni* OR carcino* OR adenocarcinoma* OR radioth* OR radiat* OR radiochemo* OR irradiat* OR chemo*) AND (stomatitis OR "Stevens Johnson syndrome" OR "candidiasis oral" OR mucositis OR (oral AND (cand* OR mucos* OR fung*)) OR mycosis OR mycotic OR thrush))

Appendix 2. CENTRAL search strategy

1. Exp NEOPLASMS
2. Exp LEUKEMIA
3. Exp LYMPHOMA
4. Exp RADIOTHERAPY
5. Exp BONE MARROW TRANSPLANTATION
6. neoplasm* or cancer* or carcino* or malignan*
7. leukemi* or leukaemia*
8. tumour* or tumor*
9. neutropeni*
10. adenocarcinoma*
11. lymphoma*
12. (radioth* or radiat* or irradiat* or radiochemo*)
13. (bone next marrow next transplant*)
14. chemo* or radiochemo*
15. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14)
16. Exp STOMATITIS
17. MUCOSITIS
18. CANDIDIASIS ORAL
19. stomatitis
20. (stevens next johnson next syndrome)
21. mucositis
22. oral near cand*
23. mouth near cand*
24. oral and fung*

25. mouth and fung*
26. (mycosis or mycotic or thrush)
27. #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
28. #15 AND #27

Appendix 3. MEDLINE via OVID search strategy

1. exp NEOPLASMS/
2. exp LEUKEMIA/
3. exp LYMPHOMA/
4. exp RADIOTHERAPY/
5. Bone Marrow Transplantation/
6. neoplasm$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
7. cancer$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
8. (leukaemi$ or leukemi$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
9. (tumour$ or tumor$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
10. malignan$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
11. neutropeni$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
12. carcino$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
13. adenocarcinoma$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
14. lymphoma$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
15. (radioth$ or radiat$ or irradiat$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
16. (bone adj marrow adj5 transplant$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
17. chemo$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
18. or/1-17
19. exp STOMATITIS/
20. Candidiasis, Oral/
21. stomatitis.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
22. mucositis.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
23. (oral and cand$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
24. (oral adj6 mucos$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
25. (oral and fung$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
26. (mycosis or mycotic).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name]
27. or/19-26

28. 18 and 27

Search filter for MEDLINE via OVID

Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (September 2009 revision) as referenced in Chapter 6 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.0.2 (updated September 2008):
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. animals.sh. not (humans.sh. and animals.sh.)
11. 9 not 10

Appendix 4. EMBASE via OVID search strategy

1. exp NEOPLASM/
2. exp LEUKEMIA/
3. exp LYMPHOMA/
4. exp RADIOTHERAPY/
5. exp bone marrow transplantation/
6. (neoplasm$ or cancer$ or leukemi$ or leukaemi$ or tumour$ or tumor$ or malignan$ or neutropeni$ or carcino$ or adenocarcinoma$ or lymphoma$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
7. (radioth$ or radiat$ or irradiat$ or radiochemo$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
8. (bone marrow adj3 transplant$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
9. chemo$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
10. or/1-9
11. exp Stomatitis/
12. Thrush/
13. (stomatitis or mucositis or (oral and candid$) or (oral adj4 mucositis) or (oral and fung$) or mycosis or mycotic or thrush).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
14. or/11-13
15. 10 and 14

Filter for EMBASE via OVID

1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.

9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18

Appendix 5. CANCERLIT (PubMed Cancer Subset) search strategy

((neoplasm* OR leukemia OR leukaemia OR leukaemia OR lymphoma* OR plasmacytoma OR "histiocytosis malignant" OR reticuloendotheliosis OR "sarcoma mast cell" OR "Letterer Siwe disease" OR "immunoproliferative small intestine disease" OR "Hodgkin disease" OR "histiocytosis malignant" OR "bone marrow transplant*" OR cancer* Or tumor* OR tumour* OR malignan* OR neutropeni* OR carcino* OR adenocarcinoma* OR radioth* OR radiat* OR radiochemo* OR irradiat* OR chemotherap*) AND (stomatitis OR "Stevens Johnson syndrome" OR "candidiasis oral" OR mucositis OR (oral AND (candid* OR mucos* OR fung*)) OR mycosis OR mycotic OR thrush))
AND
(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp]) NOT (animals [mh] NOT human [mh]))

Appendix 6. SIGLE search strategy

((neoplasm* OR leukemia OR leukaemia OR leukaemia OR lymphoma* OR plasmacytoma OR histiocytosis malignant OR reticuloendotheliosis OR sarcoma mast cell OR Letterer Siwe disease OR immunoproliferative small intestine disease OR Hodgkin disease OR histiocytosis malignant OR bone marrow transplant* OR cancer* Or tumor* OR tumour* OR malignan* OR neutropeni* OR carcino* OR adenocarcinoma* OR radioth* OR radiat* OR radiochemo* OR irradiat* OR chemo*)
AND
(stomatitis OR Stevens Johnson syndrome OR candidiasis oral OR mucositis OR (oral AND (cand* OR mucos* OR fung*)) OR mycosis OR mycotic OR thrush)
Not updated after 2005

Appendix 7. LILACS search strategy

(www.bireme.org)
((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animals AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animals AND NOT (Ct human and Ct animals)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animals AND NOT (Ct human and Ct animals)))
AND
Mh NEOPLASMS OR Tw neoplasm$ OR Tw cancer$ OR Tw carcinoma$ OR Tw tumour$ OR Tw tumor$ OR Tw malignan$ OR Tw carcino$ OR Tw nuetropeni$ OR Tw adenocarcinoma$ OR Mh leukemia OR Tw leukaemia$ OR Tw leukemi$ OR Tw

lymphoma$ OR Tw “bone marrow transplantation” OR Tw “bone marrow transplant$” OR Tw radiotherapy OR Tw radioth$ OR Tw radiat$ OR Tw irradiat$ OR Tw radiochemo$ OR Tw chemo$
AND
Mh stomatitis OR Tw stomatitis OR Mh Candidiasis-Oral OR Tw “oral candidiasis” OR (Tw candida$ AND (Tw mouth OR Tw oral)) OR Tw mucositis OR ((Tw oral OR mouth) AND Tw fung$) OR (Tw oral AND Tw candidiasis$)

Appendix 8. CINAHL via EBSCO search strategy

S1 (MH “Neoplasms+”)
S2 (MH “Leukemia+”)
S3 (MH “Lymphoma+”)
S4 (MH “Radiotherapy+”)
S5 (MH “Bone Marrow Transplantation”)
S6 neoplasm*
S7 cancer*
S8 (leukemi* or leukaemi*)
S9 (tumour* or tumor*)
S10 malignan*
S11 neutropeni*
S12 carcino*
S13 adenocarcinoma*
S14 lymphoma*
S15 (radioth* or radiat* or irradiat*)
S16 (bone N1 marrow N5 transplant*)
S17 chemo*
S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
S19 MH “Stomatitis+”
S20 MH “Candidiasis, Oral”
S21 stomatitis
S22 mucositis
S23 (oral and cand*)
S24 (oral N6 mucos*)
S25 (oral and fung*)
S26 (mycosis or mycotic)
S27 S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26
S28 S18 AND S27

Filter for CINAHL search

S1 MH Random Assignment or MH Single-blind Studies or MH Double-blind Studies or MH Triple-blind Studies or MH Crossover design or MH Factorial Design
S2 TI (“multicentre study” or “multicenter study” or “multi-centre study” or “multi-center study”) or AB (“multicentre study” or “multicenter study” or “multi-centre study” or “multi-center study”) or SU (“multicentre study” or “multicenter study” or “multi-centre study” or “multi-center study”)
S3 TI random* or AB random*
S4 AB “latin square” or TI “latin square”
S5 TI (crossover or cross-over) or AB (crossover or cross-over) or SU (crossover or cross-over)
S6 MH Placebos
S7 AB (singl* or doubl* or trebl* or tripl*) or TI (singl* or doubl* or trebl* or tripl*)
S8 TI blind* or AB mask* or AB blind* or TI mask*
S9 S7 and S8
S10 TI Placebo* or AB Placebo* or SU Placebo*

S11 MH Clinical Trials
S12 TI (Clinical AND Trial) or AB (Clinical AND Trial) or SU (Clinical AND Trial)
S13 S1 or S2 or S3 or S4 or S5 or S6 or S9 or S10 or S11 or S12

WHAT'S NEW

Last assessed as up-to-date: 8 March 2011.

Date	Event	Description
31 January 2013	Amended	Corrected error in summary of findings table 1

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 2000

Date	Event	Description
8 March 2011	New search has been performed	Updated search.
8 March 2011	New citation required and conclusions have changed	Results and conclusions changed and five summary of findings tables added
10 November 2010	New citation required and conclusions have changed	Nine interventions found to be beneficial for the prevention of mucositis. Conclusions changed
10 November 2010	New search has been performed	42 new studies and 14 new interventions added. Risk of bias assessments incorporated
16 June 2008	Amended	Converted to new review format.
21 August 2007	New citation required and conclusions have changed	Substantive amendment. This substantial update with a search only 14 months after the previous one includes 18 new included studies, bringing the total of number of studies up to 89. There are four new interventions included, bringing the total number of interventions to 33

CONTRIBUTIONS OF AUTHORS

Helen Worthington (HW) and Jan Clarkson (JC) wrote the protocol and 2000, 2003, 2006 and 2007 updates of the review.

The 2010 update was co-ordinated by Gemma Bryan (GB) and HW. GB, HW, JC independently and in duplicate assessed the eligibility of the trials. GB, HW, JC, Susan Furness (SF), Anne-Marie Glenny (A-MG), and Anne Littlewood (AL) independently and in duplicate extracted the information to complete the characteristics of included studies, and assessed the risk of bias of the trials. Data extraction was done by HW, GB, JC and AL and HW conducted the statistical analysis. GB, HW, JC, SF, A-MG, AL, Martin McCabe (MMcC) wrote the review. MMcC, Stefan Meyer (SM) and Tasneem Khalid (TK) provided a clinical perspective on the cancer, cancer treatments and interventions for preventing mucositis.

DECLARATIONS OF INTEREST

None known.

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Internal sources

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External sources

- NIDCR grant ref 1 DE016950-01, USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Clarification of the reason for exclusion of trials which report only multicomponent oral health indices.

NOTES

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

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*adverse effects]; Candidiasis, Oral [etiology; *prevention & control]; Neoplasms [*therapy]; Oral Ulcer [etiology; *prevention & control]; Randomized Controlled Trials as Topic; Stomatitis [etiology; *prevention & control]

MeSH check words

Humans