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

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[Intervention Review]

Interventions for preventing oral candidiasis 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 and treat them. One of these side effects is oral candidiasis.

Objectives

To assess the effectiveness of interventions (which may include placebo or no treatment) for the prevention of oral candidiasis for patients with cancer receiving chemotherapy or radiotherapy or both.

Search strategy

Computerised searches of Cochrane Oral Health Group and PaPaS Trials Registers, CENTRAL, MEDLINE, EMBASE, CINAHL, CANCERLIT, SIGLE and LILACS were undertaken.

Reference lists from relevant articles were searched and the authors of eligible trials were contacted to identify trials and obtain additional information.

Date of the most recent searches: 3 August 2009: CENTRAL (*The Cochrane Library* 2009, Issue 3).

Selection criteria

Trials were selected if they met the following criteria: design - random allocation of participants; participants - anyone receiving chemotherapy or radiotherapy treatment for cancer; interventions - agents prescribed to prevent oral candidiasis; primary outcome - prevention of oral candidiasis.

Data collection and analysis

Data were recorded on the following secondary outcomes if present: relief of pain, amount of analgesia, relief of dysphagia, incidence of systemic infection, duration of stay in hospital (days), cost of oral care, patient quality of life, death, use of empirical antifungal treatment, toxicity and compliance.

Information regarding methods, participants, interventions, outcome measures and results were independently extracted, in duplicate, by two review authors. The Cochrane Collaboration statistical guidelines were followed and risk ratios (RR) calculated using random-effects models. Potential sources of heterogeneity were examined in random-effects metaregression analyses.

Main results

Twenty-eight trials involving 4226 patients satisfied the inclusion criteria. Drugs absorbed and partially absorbed from the gastrointestinal (GI) tract were found to prevent oral candidiasis when compared to a placebo, or a no treatment control group, with RR for absorbed drugs = 0.47 (95% confidence interval (CI) 0.29 to 0.78). For absorbed drugs in populations with an incidence of 20% (mid range of results in control groups), this implies a number needed to treat (NNT) of 9 (95% CI 7 to 13) patients need to be treated to avoid one patient getting oral candidiasis. There was no significant benefit shown for drugs not absorbed from the GI tract.

Authors' conclusions

There is strong evidence, from randomised controlled trials, that drugs absorbed or partially absorbed from the GI tract prevent oral candidiasis in patients receiving treatment for cancer. There is also evidence that these drugs are significantly better at preventing oral candidiasis than drugs not absorbed from the GI tract.

PLAIN LANGUAGE SUMMARY

Interventions for preventing oral candidiasis for patients with cancer receiving treatment

There is strong evidence that some antifungal drugs prevent oral candidiasis (thrush) caused by cancer treatment, but nystatin does not appear to work.

Treatment for cancer can lead to severe fungal infections (thrush) in the mouth. This can cause discomfort, pain, difficulties in eating, longer stays in hospital and more worryingly, systemic infection and risk to life. Different drugs are used to try and prevent this condition. The review found strong evidence from a large number of trials that some of the antifungal drugs (those absorbed and partially absorbed into the body) help prevent fungal infections in the mouth. Some other commonly used drugs such as nystatin, which are not absorbed into the body, do not appear to work.

BACKGROUND

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

Antifungal agents are often used during the treatment of cancer to prevent superficial infections including oral candidiasis. Prevention of superficial infection is considered important because of its possible role in the development of systemic fungal infection. The incidence of systemic fungal infection has increased with the development of increasingly effective cancer therapy causing greater mucosal damage and prolonged neutropenia (De Pauw 1997). Systemic infection is difficult to diagnose early and consequently cure because it rapidly becomes well advanced and disseminated leading to considerable morbidity and mortality. Sometimes empirical antifungal treatment is given to patients without documented fungal infection but with persistent fever despite antibiotic treatment. A current Cochrane review concludes that the only prophylactic or empirical antifungal agent with documented evidence of reducing mortality in cancer patients with neutropenia is intravenous amphotericin B (Gotzsche 2002). In this review studies concerned with the prevention and treatment of oral candidiasis were excluded.

We consider it important to review the evidence for the prevention of oral candidiasis because of the effect a fungal infection in the mouth has on general well being and the possible related systemic

consequences. This review is one in a series of four Cochrane reviews evaluating the evidence for the prevention and treatment of oral candidiasis and oral mucositis in patients treated for cancer (Clarkson 2007; Worthington 2007; Worthington 2007a).

OBJECTIVES

To assess the effectiveness of interventions (which may include placebo or no treatment) for the prevention of oral candidiasis for patients with cancer, receiving chemotherapy or radiotherapy or both.

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

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

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

- Relief of pain (binary: yes/no)
- Amount of analgesia (continuous)
- Relief of dysphagia (binary: yes/no)
- Incidence of systemic infection (binary: yes/no)
- Duration of stay in hospital (days) (continuous)
- Cost of oral care (continuous)
- Patient quality of life (continuous or binary)
- Death (binary: yes/no)
- Use of empirical antifungal treatment (binary: yes/no)
- Toxicity (adverse events 'probably due to drug') (binary: yes/no)
- Compliance (binary: good versus other).

The following subgroup analyses were proposed.

- Cancer type (leukaemia, solid cancer and mixed)
- 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.

Types of participants

Anyone with cancer who received chemotherapy or radiotherapy or both.

Types of interventions

Active agents: any antifungal intervention for the prevention of oral candidiasis.
Control: may be placebo or no treatment, or another active intervention.

Types of outcome measures

The following outcome was considered in this review.

- Oral candidiasis (binary: absent or present).

The following secondary outcomes were recorded if present.

- Relief of pain (binary: yes/no)
- Amount of analgesia (continuous)
- Relief of dysphagia (binary: yes/no)
- Incidence of systemic infection (binary: yes/no)
- Duration of stay in hospital (days) (continuous)
- Cost of oral care (continuous)
- Patient quality of life (continuous or binary)
- Death (binary: yes/no)
- Use of empirical antifungal treatment (binary: yes/no)
- Toxicity (adverse events 'probably due to drug') (binary: yes/no)
- Compliance (binary: good versus other).

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.
Electronic searching - the databases searched were:
Cochrane Oral Health Group Trials Register
Cochrane Pain, Palliative and Supportive Care (PaPaS) Group Trials Register
Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 3)
MEDLINE (from 1966) and MEDLINE Pre-indexed

EMBASE (from 1974)
CINAHL
CANCERLIT via PubMed
OPEN SIGLE
LILACS.

Sensitive search strategies were developed for each database using a combination of free text and MeSH terms. These are described in detail in Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7 and Appendix 8.

Only handsearching carried out by The Cochrane Collaboration is 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, SIGLE, and LILACS.

Date of most recent searches: 03.08.09 (CENTRAL) (*The Cochrane Library* 2009, Issue 3), MEDLINE 03.08.09, EMBASE 03.08.09, CINHAL 03.08.09, LILACS 03.08.09, CANCER LIT 03.08.09, OHG Register 03.08.09, Papas Register 29.07.09.

Data collection and analysis

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

Quality assessment

The quality assessment of the included trials was undertaken independently and in duplicate by two review authors as part of the data extraction process.

Three main quality criteria were examined.

(1) Allocation concealment, recorded as:
(A) Adequate
(B) Unclear
(C) Inadequate as described in the *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5.

(2) Treatment blinded to outcome assessors, patients and providers recorded as:
(A) Yes
(B) No
(C) Unclear
(D) Not possible.

(3) Completeness of follow up (is there a clear explanation for withdrawals and drop outs in each treatment group?) assessed as:
(A) Yes
(C) No.

After taking into account the additional information provided by the authors of the trials, studies were grouped into the following categories based on three criteria: allocation concealment, treatment blinded to outcome assessor and completeness of follow up:

(A) Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met.

(B) Moderate risk of bias (plausible bias that raises some doubt about the results) if one of the criteria was not met.

(C) High risk of bias (plausible bias that seriously weakens confidence in the results) if two or more criteria were not met as described in the *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5 section 6.7.

Further quality assessment was carried out to assess sample size calculations, definition of exclusion/inclusion criteria, and comparability of control and test groups at entry. The quality assessment criteria were pilot tested using several articles.

The quality assessment of included trials was undertaken independently and in duplicate by two review authors as part of the data extraction process. Included trials were assessed on the following criteria: concealed allocation of treatment; blinding of patients, carers and outcome assessors; and information on reasons for withdrawal by trial group. The risk of bias was assessed as high, moderate or low, according to the *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5. The agreement between the review authors was assessed by calculating the Kappa score.

Data were extracted by two review authors independently using specially designed data extraction forms. The characteristics of the trial participants, interventions and outcomes for the included trials are presented in the study tables. The incidence of oral candidiasis was measured in several different ways ranging from clinical examination to mycological assessment. The clinical assessment was used if present otherwise the mycological assessment was included. Oral candidiasis was recorded as absent or present, and the 'Characteristics of included studies' table includes a description of the methods of measurement used. The duration of trials was recorded along with interim assessments and a decision made about which to use to maximise commonality. We also recorded the country where the trial was conducted, which year it was published and whether a dentist was involved in the investigation. Authors were contacted for clarification or for further information.

We decided a priori to categorise the interventions as whether they were fully absorbed, partially absorbed or not absorbed from the gastrointestinal (GI) tract.

Data synthesis

For dichotomous outcomes, the estimates of effect of an intervention was expressed as risk ratios together with 95% confidence intervals. Where there were studies of similar comparisons reporting the same candidiasis outcome measure a meta-analysis was undertaken. Risk ratios were combined for the dichotomous data, and mean differences combined for continuous data, both using a random-effects model.
The significance of any discrepancies in the estimates of the treatment effects from the different trials was assessed by means of Cochran's test for heterogeneity, and the I^2 statistic, where I^2 describes the percentage of total variation across studies that is due to heterogeneity rather than chance. Any heterogeneity was fully investigated.

Investigation of publication and other biases

A funnel plot (plots of effect estimates versus the inverse of their standard errors) was drawn. Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size, though it may also represent a true relationship between trial size and effect size. A formal investigation of the degree of asymmetry was performed using the method proposed by Egger et al (Egger 1997). A further method proposed by Begg and Mazumdar which tests for publication bias by determining if there is a significant correlation between the effect estimates and their variances was also carried out (Begg 1994). Both methods were carried out using Stata version 7.0 (Stata Corporation, USA) using the program Metabias.

It was planned to undertake a sensitivity analysis to examine the effect of concealed allocation, blinded outcome assessment and assessment of study as of low risk of bias on the overall estimates of effect. We also proposed a priori to conduct subgroup analyses for different cancer types (solid, leukaemia and mixed) and age groups (children, adults and mixed). These analyses were undertaken using random-effects metaregression, using the Stata version 7.0 (Stata Corporation, USA) using the program Metareg (Sharp 1998).

RESULTS

Description of studies

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

Characteristics of the trial setting and investigators

Of the 112 potentially eligible trials, 82 studies were excluded for the following reasons:

- no oral outcome or data in the wrong form (34 trials);
- the data were presented as episodes not patients (10 trials);
- used as empirical therapy only treating patients with infection (nine trials);
- abstracts with insufficient information (five trials);
- not a randomised controlled trial or this was unclear (17 studies);
- liver transplant patients (one trial);
- inappropriate study design (five trials);
- study halted early (one trial).

Of the 28 included trials, nine were conducted in North America (Bodey 1990; Buchanan 1985; Cuttner 1986; Epstein 1992; Ferretti 1988; Owens 1984; Vogler 1987; Winston 1993; Yeo 1985), 16 in Europe (Brincker 1978; Brincker 1983; Caselli 1990; Egger 1995; Giorgis 1991; Hann 1982; Huijgens 1999; Menichetti 1994; Menichetti 1999; Ninane 1994; Orlandi 1986; Palmblad 1992; Philpott-Howard 1993; Rozenberg-Arska 1991; Wahlin 1989; Williams 1977), and a further three, one in South Africa (Scrimgeour 1985), one in Brazil (Nucci 2000) and one in Japan (Yamada 1993). All trials had a parallel group study design. The trials were published in 34 reports between 1977 and 2000 with two trials published in the 1970s, 13 in the 1980s, 18 in the 1990s, and one trial since 2000. Five were multicentre studies (Menichetti 1994; Menichetti 1999; Ninane 1994; Philpott-Howard 1993; Winston 1993) and six studies had more than one publication. Eighteen of the trials received external funding, three trials did not and this was unclear in the remaining seven. The percentage of patients lost to follow up ranged from 0% to 81%, with a median value of 5%. Eight studies reported no drop outs and this included two large multicentre studies (Brincker 1983; Buchanan 1985; Caselli 1990; Cuttner 1986; Menichetti 1994; Menichetti 1999; Wahlin 1989; Williams 1977). The providers and assessors of the treatments were mainly medical staff though three of the trials clearly involved a dentist (Epstein 1992; Ferretti 1988; Wahlin 1989) but in no trial were patients involved in the outcome measurement. Two further studies are awaiting classification (Corvo 2008; Elad 2006).

Characteristics of the participants

Seventeen of the 28 trials recruited only adult patients with cancer, eight included both adults and children, two included only child patients (Caselli 1990; Ninane 1994) and in one trial the age of the patients was unclear (Scrimgeour 1985). The type of cancer being treated was leukaemia in 18 trials, solid tumours in three trials and a combination of both in seven trials.

Characteristics of the interventions

All of the 28 trials provided a clear description of the interventions including the dose and method of administration for both the test and control group. Eleven trials included a placebo control group, a further six a 'no treatment' control group, and one trial had a group using a saline rinse (Epstein 1992). Eight trials compared different test agents with varying doses, frequency and duration of use. One trial compared different doses of the same test agent (Scrimgeour 1985).

The interventions for the 28 trials assessing the treatment of oral candidiasis were categorised according to the degree of absorption from the gastrointestinal (GI) tract.

Absorbed from the GI tract

- Fluconazole (Bodey 1990; Egger 1995; Huijgens 1999; Menichetti 1994; Ninane 1994; Philpott-Howard 1993; Rozenberg-Arska 1991; Winston 1993)
- Ketoconazole (Brincker 1983; Caselli 1990; Hann 1982; Palmblad 1992; Scrimgeour 1985; Vogler 1987)
- Itraconazole (Caselli 1990; Huijgens 1999; Menichetti 1999; Nucci 2000).

Partially absorbed from the GI tract

- Miconazole (Brincker 1978)
- Clotrimazole (Cuttner 1986; Owens 1984; Yeo 1985).

Not absorbed from the GI tract

- Amphotericin B (Caselli 1990; Menichetti 1994; Orlandi 1986; Rozenberg-Arska 1991; Yamada 1993)
- Nystatin (Buchanan 1985; Egger 1995; Epstein 1992; Vogler 1987; Williams 1977)
- Chlorhexidine (Epstein 1992; Ferretti 1988; Wahlin 1989)
- Nystatin + chlorhexidine (Epstein 1992)
- Thymostimulin (Giorgis 1991)
- Amphotericin B + nystatin (Hann 1982)
- Polyenes (amphotericin B or nystatin) (Ninane 1994; Philpott-Howard 1993)
- Natamycin (Williams 1977)
- Norfloxacin + amphotericin B (Yamada 1993).

The trials assessing absorbed drugs are generally more recent (1982 to 2000) than those for either partially absorbed drugs (1978 to 1986) or those for drugs not absorbed (1977 to 1995).

Characteristics of outcome measures

There was variation between the trials in the assessment of oral candidiasis. Three trials just reported a clinical assessment of oral candidiasis (Brincker 1983; Williams 1977; Yamada 1993), six trials only a mycological assessment (Buchanan 1985; Caselli 1990; Cuttner 1986; Epstein 1992; Giorgis 1991; Winston 1993), and 19 trials presented both types of assessment frequently with the clinical assessment being confirmed by a mycological assessment. The percentage of patients developing candidiasis in the 19 control or no treatment groups ranged from 5% to 100%, with a median value of 50%.

Several other outcomes were recorded, by study group, in some of the trial reports. Systemic fungal infection was recorded in 17 studies (Brincker 1983; Caselli 1990; Egger 1995; Ferretti 1988; Hann 1982; Huijgens 1999; Menichetti 1994; Menichetti 1999; Ninane 1994; Nucci 2000; Owens 1984; Palmblad 1992; Philpott-Howard 1993; Rozenberg-Arska 1991; Vogler 1987; Winston 1993; Yamada 1993) and this ranged across study groups from 0% to 46%. Death associated with fungal infection was recorded in eight trials (0% to 11%) (Egger 1995; Ferretti 1988; Hann 1982; Huijgens 1999; Menichetti 1994; Menichetti 1999; Nucci 2000; Palmblad 1992), empirical antifungal treatment in eight trials (0% to 74%) (Egger 1995; Hann 1982; Huijgens 1999; Menichetti 1994; Nucci 2000; Owens 1984; Rozenberg-Arska 1991; Winston 1993), toxicity due to adverse events 'probably due to treatment' in 13 trials (0% to 18%) (Cuttner 1986; Egger 1995; Huijgens 1999; Menichetti 1994; Menichetti 1999; Ninane 1994; Nucci 2000; Owens 1984; Philpott-Howard 1993; Rozenberg-Arska 1991; Scrimgeour 1985; Vogler 1987; Winston 1993) and good compliance in five trials (72% to 99%) (Egger 1995; Huijgens 1999; Menichetti 1994; Menichetti 1999; Nucci 2000).

Risk of bias in included studies

The concealment of allocation was adequate for 13 (46%) of the 28 trials but it was unclear for the remaining 15 (Additional Table 1). The outcome assessor was blinded in 16 trials (57%), not blinded in four trials and masking was unclear in the remaining eight trials. The withdrawals were adequately reported in 18 trials (64%) and were unclear or not reported in the remainder. The Kappa scores between the two raters were: 0.70 for allocation concealment, 0.39 for blinding of outcome assessor, 0.46 for clear information about withdrawals.

Table 1. Quality assessment of included studies

Study	Concealed allocation	Patient blinded	Provider blinded	Outcome blinded	Clear withdrawals	Risk of bias
Bodey 1990	adequate	yes	yes	yes	no	moderate
Brincker 1978	adequate	yes	yes	yes	yes	low
Brincker 1983	adequate	yes	yes	yes	yes	low
Buchanan 1985	unclear	no	no	unclear	yes	high
Caselli 1990	unclear	no	no	yes	yes	moderate
Cuttner 1986	adequate	yes	yes	yes	yes	low
Egger 1995	unclear	no	no	unclear	no	high
Epstein 1992	adequate	no	no	unclear	no	high
Ferretti 1988	adequate	yes	yes	yes	no	moderate
Giorgis 1991	unclear	yes	no	no	yes	high
Hann 1982	unclear	no	no	yes	yes	moderate
Huijgens 1999	unclear	yes	yes	yes	no	high
Menichetti 1994	unclear	no	no	unclear	yes	high
Menichetti 1999	unclear	yes	yes	yes	yes	moderate
Ninane 1994	unclear	no	no	unclear	no	high
Nucci 2000	adequate	yes	yes	yes	yes	low
Orlandi 1986	unclear	no	no	unclear	yes	high
Owens 1984	adequate	yes	yes	yes	no	moderate
Palmblad 1992	unclear	yes	yes	yes	yes	moderate
Philpott-Howard 1993	unclear	no	no	unclear	yes	high
Rozenberg-Arska 1991	unclear	no	no	unclear	no	high

Table 1. Quality assessment of included studies (*Continued*)

Scrimgeour 1985	unclear	unclear	unclear	unclear	no	high
Vogler 1987	unclear	no	no	unclear	yes	high
Wahlin 1989	adequate	no	no	yes	yes	low
Williams 1977	adequate	no	no	no	yes	moderate
Winston 1993	unclear	yes	yes	yes	yes	moderate
Yamada 1993	unclear	no	no	unclear	yes	high
Yeo 1985	adequate	no	no	yes	no	moderate

Letters were sent to authors of the trials and replies were received from the authors of 12 included and one excluded study, the information supplied changed the concealment of allocation from unclear to adequate in eight studies, and clarified the reasons for withdrawal, or missing data.

Five studies were assessed as at low risk of bias (Brincker 1978; Brincker 1983; Cuttner 1986; Nucci 2000; Wahlin 1989), 10 at moderate risk and 12 at high risk of bias (Additional Table 1).

Effects of interventions

Electronic searches identified over 6000 titles and abstracts and from this we obtained over 400 full reports for the four reviews in this series. One hundred and nine studies were considered eligible for this review according to the defined criteria for trial design, participants, interventions and outcomes. Of these 81 trials were excluded for reasons summarised in the Description of studies section.

For the 28 trials included in the review the results are based on 4226 patients who were assessed for oral candidiasis. The range of patients was from eight to 420 per treatment/control group.

Comparisons with placebo/no treatment: oral candidiasis (comparison 1, outcome 1.1)

Seven trials involving 1153 patients compared drugs absorbed from the gastrointestinal (GI) tract with placebo, or 'no treatment' control group and the meta-analysis showed that these drugs prevented oral candidiasis with risk ratio (RR) of 0.47 (95% confidence interval (CI) *Random Effects* 0.29 to 0.78, Chi^2 = 10.2, degrees of freedom (df) = 6, P = 0.12, I^2 = 41%). In order to illustrate the magnitude of the effect, the number of patients needed to treat (NNT) to prevent one patient getting oral candidiasis were calculated, based on this pooled effect estimate and on the incidence of oral candidiasis in the control groups of the trials that contributed data to this meta-analysis. The incidence was 5% to 60%, median value 20%. In populations with a low incidence of oral candidiasis of 5%, this gives a NNT of 37 (95% CI 29 to 56) patients requiring treatment to avoid one patient getting oral candidiasis during the cancer treatment period. In populations with an incidence of 20% (mid range of results in control groups), this implies a NNT of 9 (95% CI 7 to 13) patients requiring treatment to avoid one patient getting oral candidiasis. For populations with a high incidence (60%) the NNT is 3 (95% CI 3 to 5).

Four trials involving 292 patients compared drugs partially absorbed from the GI tract with placebo and these drugs were also found to prevent oral candidiasis (RR = 0.13, 95% CI *Random Effects* 0.06 to 0.46, Chi^2 = 5.3, df = 3, P = 0.15, I^2 = 43%).

Eight studies involving 382 patients compared drugs not absorbed from the GI tract with placebo or no treatment control groups, and overall the drugs did not have a significant benefit in preventing oral candidiasis RR = 0.68 (95% CI 0.46 to 1.02, Chi^2 for heterogeneity = 23.3, df = 7, P < 0.001, I^2 = 70%). Since 70% of the total variation across studies is due to heterogeneity rather than

chance this was investigated. Subgroup analyses were conducted for age group and cancer type and these factors failed to explain the large heterogeneity present for the eight studies involving the non-absorbed drugs, however, this was investigated further in a meta-analysis presented later in this section.

Comparisons with placebo/no treatment: other outcomes (comparison 1, outcomes 1.2-1.6)

Significantly more control patients were given empirical antifungal treatment than patients receiving drugs absorbed from the GI tract, RR = 0.85 (95% $CI_{Random\ Effects}$ 0.73 to 0.99, Chi^2 = 0.55, df = 1, P = 0.46, I^2 = 0%) (outcome 1.4). There were no significant differences between patients receiving antifungal drugs in any category compared with placebo or 'no treatment' for the following outcomes: systemic fungal infection, death, toxicity and compliance (outcomes 1.2, 1.3, 1.5, 1.6).

Comparisons between drugs absorbed from the GI tract and those not absorbed: oral candidiasis (comparison 2, outcome 2.1)

Nine studies compared drugs absorbed from the GI tract directly with those not absorbed, although there were no participants with candidiasis in one trial, so the data from eight studies were included. The meta-analysis showed a significant benefit in using the absorbed drugs rather than those not absorbed to prevent oral candidiasis with RR = 0.40 (95% $CI_{Random\ Effects}$ 0.21 to 0.76, Chi^2 for heterogeneity = 12.5, df = 6, P = 0.052, I^2 = 51.9%).

Comparisons between drugs absorbed from the GI tract and those not absorbed: other outcomes (comparison 2, outcomes 2.2-2.6)

There were no significant differences between patients receiving either absorbed or drugs not absorbed from the GI tract for the following outcomes: systemic fungal infection, death, empirical antifungal treatment, toxicity and compliance (outcomes 2.3, 2.4-2.6).

Comparison of drugs absorbed from the GI tract: oral candidiasis (comparison 3, outcome 3.1)

Three trials compared different drugs absorbed from the GI tract. One study compared itraconazole with fluconazole finding no evidence of a difference (Huijgens 1999). Another study compared ketoconazole with itraconazole also finding no difference (Caselli 1990). A further study compared two doses of ketoconazole 200 mg and 400 mg (Scrimgeour 1985), however as none of the patients experienced oral candidiasis the results of the study have no value.

Comparison of drugs absorbed from the GI tract: other outcomes (comparison 3, outcomes 3.2-3.6)

There were no significant differences for any of the other outcomes.

Comparison of drugs not absorbed from the GI tract: oral candidiasis (comparison 4, outcome 4.1)

Three trials compared different drugs which were not absorbed from the GI tract. One study compared three groups of patients using chlorhexidine, nystatin, and chlorhexidine plus nystatin (Epstein 1992). The two other studies compared nystatin with natamycin (Williams 1977), and norfloxacin plus amphotericin B with amphotericin B (Yamada 1993). There was no evidence of a difference between the drugs for the first two studies and a borderline effect for the norfloxacin study, with fewer patients in the norfloxacin group getting oral candidiasis (P = 0.05). Only one of these studies reported another outcome, systemic infection, which was not significant with RR = 0.67 (95% CI 0.20 to 2.23) (Yamada 1993). No other outcomes (systemic fungal infection, death, empirical antifungal treatment, toxicity or compliance) were reported in these studies.

Publication bias

Publication bias was assessed for the primary outcome, oral candidiasis, for three groups of trials:

- drugs absorbed from GI tract versus placebo (7 trials, comparison 1, outcome 1.1);
- drugs not absorbed from GI tract versus placebo (8 trials, comparison 1, outcome 1.1);
- absorbed drugs versus drugs not absorbed (7 trials, comparison 2, outcome 2.1).

The funnel plot for each appeared asymmetric and there is evidence of bias for all three groups of studies using the Egger (weighted regression) method (P = 0.003, < 0.001, 0.018, respectively), but not using the Begg (rank correlation) method (P = 0.65, 0.30, 0.22) (Begg 1994; Egger 1997).

Metaregression

See Additional Table 2.

Metaregression models were fitted, using Stata version 7, to investigate how much of the heterogeneity of treatment effect is explained by drug type (three categories), age group (three categories) and cancer type (three categories) for the 19 comparisons in 18 placebo controlled or no treatment control trials. A univariate analysis for drug type showed significant differences for both

the absorbed (P = 0.016) and partially absorbed drugs (P = 0.002) when compared with the non-absorbed drugs, the drugs absorbed or partially absorbed from the GI tract being more effective (Additional Table 2). It is recognised that there are weaknesses in using indirect comparisons, however, the indirect comparison for absorbed drugs did support the findings of the direct comparison (comparison 2, outcome 2.1). The model for age group (including drug type) showed no significant differences in the effect size for the different age groups however the model for cancer type (including drug type) showed a significant difference between cancer types, with the treatment effect being greater for trials including patients with blood (P = 0.032) and mixed cancers (P = 0.031) compared to those including patients with solid cancer. Further metaregression models were fitted for both allocation concealment and outcome assessment blinded (including drug type), and no significant difference in effect size was found between studies assessed as adequate or not for either of these quality assessments.

Table 2. Random-effects metaregression for placebo and no treatment controlled trials

Comparison	Co-efficient	95% CI	P value	Interpretation
Non-absorbed versus absorbed drugs	-0.47	-0.85, -0.09	0.016	benefit (prevention of oral candidiasis) greater for absorbed drugs
Non-absorbed versus partially absorbed drugs	-1.23	-2.02, -0.45	0.002	benefit greater for partially absorbed drugs
Mixed age versus adults	0.16	-0.12, 0.44	0.27	no significant difference
Children versus adults	-0.01	-0.74, 0.73	0.98	no significant difference
Solid versus blood cancer	1.12	0.10, 2.14	0.032	benefit greater for patients with blood cancer
Solid versus mixed cancer	1.18	0.11, 2.25	0.031	benefit greater for patients with mixed cancer
Concealed allocation (yes versus no)	-0.05	-0.35, 0.26	0.77	no significant difference
Outcome assessment blinded (yes versus no)	-0.34	-0.88, 0.21	0.23	no significant difference

A sensitivity analysis was proposed for studies at low risk of bias. Five studies were categorised as this, but only one in each of the classes of drugs for the comparisons between drugs and placebo or no treatment. For absorbed drugs (Brincker 1983) the RR was 0.25 (95% CI 0.06 to 1.03), for partially absorbed drugs (Cuttner 1986) the RR was 0.09 (95% CI 0.01 to 0.65) and for drugs not absorbed (Wahlin 1989) the RR was 0.89 (95% CI 0.79 to 1.02) so the results were similar to those for all studies.

A priori we decided to categorise the drugs into three categories: absorbed, partially absorbed and not absorbed from the GI tract. When comparing drugs in each of these categories with placebo or 'no treatment' controls it was found that there was significant heterogeneity for the not absorbed category of drugs, whereas the other two categories were fairly homogeneous. In order to investigate this heterogeneity further, the eight comparisons involving not absorbed drugs can be categorised further into drug types: nys-

tatin (two trials), amphotericin B (two trials), chlorhexidine (three trials) and thymostimulin (one trial). The comparisons between the groups were not significant in a metaregression analysis (nystatin versus amphotericin B, P = 0.09; nystatin versus chlorhexidine, P = 0.41; nystatin versus thymostimulin, P = 0.18). However classification by drug type did appear to reduce the heterogeneity, although there are only a few trials in each category. The meta-analysis shown in MetaView (comparison 5, outcome 5.1) indicates that there may be some benefit for amphotericin B with RR = 0.43 (95% CI 0.20 to 0.94), whereas there is no evidence of a benefit for nystatin.

DISCUSSION

We have found evidence that antifungal agents absorbed from the gastrointestinal tract prevent oral candidiasis in patients receiving treatment for cancer. Drugs fully absorbed (fluconazole, ketoconazole and itraconazole) and partially absorbed (miconazole and clotrimazole) are effective compared with placebo or no treatment. The quality of the trials was mixed, however no differences in effect size were found when poor quality studies were excluded. There is no evidence that overall the group of non-absorbed drugs are effective and looking at these drugs individually this finding is consistent for the commonly prescribed oral polyene, nystatin, however, there is weak evidence that amphotericin B might be of benefit. Both direct and indirect comparisons demonstrate the superiority of absorbed compared with non-absorbed drugs to prevent superficial oral fungal infections. However, it is not possible to assess the importance in terms of effectiveness, of how long drugs are retained in the mouth, or the local or systemic concentrations.

No trial reported outcomes related to general well being such as relief of pain, relief of dysphagia, amount of analgesia, days stay in hospital and patient quality of life. It is therefore difficult to comment on the importance of these patient based outcomes although, they are frequently cited as justification for the conduct of trials. Neither is it possible to comment on the cost of oral care as no trial reported either specific or comparative data. It is not possible to assess the association between oral candidiasis and systemic infection from the data presented. However, from trials reporting systemic outcomes, the prophylactic use of absorbed drugs reduced the proportion of patients receiving empirical antifungal treatment compared with control patients (two trials).

For patients being treated for cancer the clinical dilemma is whether to prevent, treat or leave oral candidiasis. The findings from our reviews demonstrate that oral candidiasis can be effectively prevented, however the evidence for effective treatment is weaker and unreliable (Worthington 2007). Compared with this review, which includes evidence from over 4000 patients, the treatment review included trials on around 400 patients and only two agents were found to be effective (ketoconazole and clotrimazole) each in single trials. The decision to use antifungal agents to prevent or treat superficial oral infections requires consideration of the risks and benefits. In this review toxicity due to adverse events 'probably due to treatment' was documented in 13 trials of the 28 included trials and ranged from 0% to 18%, however little information was given concerning the nature and severity of the toxicity. More careful documentation of this in future trials included in both reviews would help to evaluate the possible risks of these interventions.

The incidence of oral candidiasis is variable and depends primarily on the nature of the underlying disease and the intensity of treatment. The incidence in control groups included in this review ranges from 5% to 100%, with a median value of 50%. The generalizability of the results is difficult to comment on as the trials were mainly adults with blood cancer, with few studies including children, although the metaregression did indicate possible differences in effect with different cancer types. Since there is no evidence of an effect on general well being to support the decision to prevent oral candidiasis, and there is weak evidence that effective prophylaxis is associated with a reduction in systemic disease, other factors require consideration. If the incidence of oral candidiasis for a patient subgroup is likely to be high, and it is considered important to prevent the disease, then a drug absorbed or partially absorbed from the gastrointestinal tract should be prescribed at the start of cancer treatment. Factors for which we have little information and further evidence is required are: the implications of drug toxicity, development of microbial drug resistance and the cost of treatment.

Whilst most of the trials report similar criteria for the diagnosis of oral candidiasis the validity of these descriptions requires consideration and a consensus on how to diagnose and report events in future trials would improve the synthesis of evidence. Epidemiological data and more consistent microbiological reporting would assist our understanding of the importance of this disease. There is some evidence that there may be publication bias, with an under reporting of small trials showing no treatment effect. It is difficult to assess the impact of this on the results of this review, however, the fact that we found such bias indicates the importance for researchers to publish the results of all trials.

The findings of this review should be considered in the context of the general medical management of patients with cancer.

AUTHORS' CONCLUSIONS

Implications for practice

For patients being treated for cancer the clinical dilemma is whether to prevent, treat or leave oral candidiasis. For treating or preventing oral candidiasis, drugs absorbed from the gastrointestinal tract should be prescribed. Overall there is no evidence that

drugs not absorbed are effective, however there is weak evidence that amphotericin B may possibly be of benefit.

Implications for research

Consideration needs to be given to developing and standardising clinical diagnostic criteria and the use of patient based outcomes.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bodey 1990

Methods	Randomised, parallel group study conducted in USA. Patient, provider and assessor blinded. Unclear information on reasons for withdrawal. Dentist not involved in the study. Drop outs: 23%.
Participants	Adults with solid cancer. 146 eligible patients, with 112 completing.
Interventions	2 groups, placebo versus fluconazole (50 mg once per day from 48 hours of admission). Duration: 4 weeks.
Outcomes	Both clinical and mycological assessment of oral candidiasis at 4 weeks. Other outcomes: none.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Brincker 1978

Methods	Randomised, parallel group study conducted in Denmark. Patient, provider, assessor blinded. Clear information on reasons for withdrawal. Dentist not involved in the study. Drop outs: 17%.
Participants	Adults with blood cancer. 30 eligible patients, 30 enrolled and 25 completed.
Interventions	2 groups, placebo versus miconazole (500 mg 4 times per day (250 mg tablets)). Duration: at least 3 weeks (max 25 days).
Outcomes	Both clinical and mycological assessment of oral candidiasis at 3 weeks, maximum 25 days. Other outcomes: none.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Brincker 1983

Methods	Randomised, parallel group study conducted in Denmark. Patient, carer, assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 0%.
Participants	Adults with blood cancer. 38 patients enrolled, 38 completed.
Interventions	2 groups, placebo versus ketoconazole (400 mg per day). Duration: 4 weeks.
Outcomes	Clinical assessment of oral candidiasis at 4 weeks. Other outcomes: systemic fungal infection.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Buchanan 1985

Methods	Randomised, parallel group study conducted in Canada. Patient and provider not blinded, unclear if assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 0%.
Participants	Adults with mixed cancer. 164 eligible patients, 78 enrolled and 78 completed.
Interventions	2 groups, control = no treatment versus nystatin (1 million units as suspension (100,000 u/ml every 4 hours). Gargle for 3 to 5 minutes before swallowing). Duration: 8 weeks.
Outcomes	Mycological assessment of oral candidiasis at 8 weeks. Other outcomes: none.
Notes	All patients had oral trimethoprim and sulfamethoxazole.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Caselli 1990

Methods	Randomised, parallel group study conducted in Italy. Patient, carer not blinded, assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 0%.
Participants	Children with blood cancer. 40 patients eligible, enrolled, and completed.

Caselli 1990 (*Continued*)

Interventions	4 groups, control = no treatment versus itraconazole (2 mg/kg daily), ketoconazole (5 mg/kg daily), amphotericin-B (50 mg/kg daily in 2 doses). Duration: 4 weeks.
Outcomes	Mycological assessment of oral candidiasis at 4 weeks. Other outcomes: systemic fungal infection.
Notes	All receiving prophylactic cotrimoxazole (thrimetoprim 5 mg/kg daily).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Cuttner 1986

Methods	Randomised, parallel group study conducted in USA. Patient, carer, assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs 0%.
Participants	Adults with blood cancer. 42 eligible patients, 28 enrolled and 28 completed. Patients had negative smears for entry into study.
Interventions	2 groups placebo versus clotrimazole (10 mg troche 3 times per day, dissolved for 15 to 30 minutes, then swallowed). Duration: 8 weeks.
Outcomes	Mycological assessment of oral candidiasis at 8 weeks. Other outcomes: toxicity (adverse events 'probably due to drug').
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Egger 1995

Methods	Randomised, parallel group study conducted in Switzerland. Patient, carer not blinded, oucome assessor blinded. Unclear which group the 1 withdrawal was in. Drop outs: 1%.
Participants	Adults and children > 14 with blood cancer. 90 randomised, 1 not evaluable as cultures after randomisation were positive for Aspergillus, but unclear which group he was in, 157 eligible. 30 patients had allogenic and 3 autologous bone marrow transplants.

Egger 1995 (*Continued*)

Interventions	2 groups high dose oral/intravenous fluconazole (400 mg daily) versus nystatin suspension (24x10E6 units 3 times per day) plus miconazole (Daktarin) inhalations 3 times daily for 10 minutes.
Outcomes	Mycological assessment of oral candidiasis at 2 weeks. Other outcomes: systemic fungal infection, death associated with fungal infection, empirical antifungal treatment, toxicity (adverse events 'probably due to drug'), good compliance.
Notes	Patients admitted to isolation unit. Nystatin administration difficult for patients receiving therapy for more than 2 weeks.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Epstein 1992

Methods	Randomised, parallel group study conducted in Canada. Patient and provider not blinded, unclear if assessor blinded. Unclear information on reasons for withdrawal. Dentist involved in the study. Drop outs: 13%.
Participants	Adults with blood cancer. 99 patients eligible and enrolled and 86 completed.
Interventions	4 groups, control = saline (15 ml rinse) versus chlorhexidine (0.2% 15 ml rinse), nystatin (100,000 u/ml 15 ml rinse), chlorhexidine + nystatin (as above). All interventions were used 4 times daily for 1 minute. Duration: 3 weeks.
Outcomes	Mycological assessment of oral candidiasis at 3 weeks. Other outcomes: none.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ferretti 1988

Methods	Randomised, parallel group study conducted in USA. Patient, provider and assessor blinded. Unclear information on reasons for withdrawals. Dentist involved in the study. Drop outs: 9%.
Participants	Adults and children with blood cancer. 56 enrolled and 51 completed.
Interventions	2 groups placebo versus chlorhexidine (15 ml for 30 seconds 3 times daily). Duration: up to 90 days.

Ferretti 1988 (*Continued*)

Outcomes	Both clinical and mycological assessment of oral candidiasis at 9 weeks. Other outcomes: systemic fungal infection, death associated with fungal infection.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Giorgis 1991

Methods	Randomised, parallel group study conducted in Italy. Patient blinded, provider and assessor not blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 27%.
Participants	Adults with solid cancer. 48 eligible and enrolled, 13 died and 35 completed.
Interventions	2 groups placebo versus thymostimulin (50 to 70 mg twice per week) Duration: 4 to 9 months.
Outcomes	Mycological assessment of oral candidiasis at 52 weeks. Other outcomes: none.
Notes	Translated from Italian.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hann 1982

Methods	Randomised, parallel group study conducted in UK. Patient and provider not blinded, assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 5%.
Participants	Adults and children with mixed cancer. 76 patients eligible, enrolled and 72 completed.
Interventions	2 groups, ketoconazole (400 mg/day in adults, 200 mg/day in children) versus amphotericin B lozenges (10 mg 4 times daily) + nystatin tablets (0.5 megaunits twice daily + nystatin suspension (0.1 megaunits twice daily). Duration: 9 weeks.
Outcomes	Both clinical and mycological assessment of oral candidiasis at 9 weeks or when neutrophil count was > 1x10E9/l. Other outcomes: systemic fungal infection, death associated with fungal infection, empirical antifungal treatment.

Hann 1982 (*Continued*)

Notes	Patients were given oral neomycin sulphate (500 mg twice daily), colistin (1.5 megaunits twice daily), trimoxazole (trimethoprim 160 mg plus sulphamethoxazole 800 mg every 12 hours).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Huijgens 1999

Methods	Randomised, parallel group study conducted in Holland. Patient, provider and assessor blinded. Unclear information on reasons for withdrawal. Dentist not involved in the study. Drop outs: 5%.
Participants	Adults with blood cancer. 213 patients enrolled and 202 completed.
Interventions	2 groups fluconazole (50 mg twice daily) versus itraconazole (100 mg twice daily). Duration: 10 to 12 days.
Outcomes	Both clinical and mycological assessment of oral candidiasis at 10-12 days. Other outcomes: systemic fungal infection, death associated with fungal infection, empirical antifungal treatment, toxicity (adverse events 'probably due to drug'), compliance.
Notes	Patients received ciprofloxacin 500 mg twice daily, roxitromycin 150 mg twice daily. Nasal amphotericin was given 2 mg 3 times per day.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Menichetti 1994

Methods	Randomised, parallel group multicentre study conducted in Italy. Patient and provider not blinded, unclear if assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 0%.
Participants	Adults and children with blood cancer. 820 eligible patients in 30 centres, 820 completed.
Interventions	2 groups fluconazole (150 mg once daily capsule) versus amphotericin B suspension (500 mg every 6 hours). Started interventions 1 to 3 days prior to chemo.
Outcomes	Both clinical and mycological assessment of oral candidiasis when neutrophil count was > 1000/uL. Other outcomes: systemic fungal infection, death associated with fungal infection, empirical antifungal treatment, toxicity (adverse events 'probably due to drug'), compliance.

Menichetti 1994 (*Continued*)

Notes	All patients received oral ciprofloxacin 500 mg twice daily).	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Menichetti 1999

Methods	Randomised, parallel group multicentre study conducted in Italy. Patient, provider and assessor blinded. Clear information on withdrawals. Unclear whether dentist was involved in the study. Drop outs: 0%.	
Participants	Adults with blood cancer. 405 eligible patients in 39 centres. 405 completed.	
Interventions	2 groups placebo versus itraconazole (oral solution 2.5 mg/kg daily, 100 mg of itraconazole per 10 ml of cyclodextrin). Started intervention 1 to 3 days before chemo. Duration: 8 weeks maximum.	
Outcomes	Both clinical and mycological assessment of oral candidiasis when neutrophil count was > 1000/uL, maximum 8 weeks. Other outcomes: systemic fungal infection, death associated with fungal infection, toxicity (adverse events 'probably due to drug'), compliance.	
Notes	All patients received nystatin 500,000 U 4 times a day, and oral ciprofloxacin 500 mg twice daily.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Ninane 1994

Methods	Randomised, parallel group multi-centre study conducted in Europe. Patient, provider and assessor blinded (c). Clear information on withdrawals 'may have been associated with side effects' (c) . Dentist not involved in the study. Drop outs: 3%.
Participants	Children with mixed cancer. 502 patients enrolled and 485 completed.
Interventions	2 groups, fluconazole suspension (3 mg/kg body weight) versus polyenes (nystatin oral suspension 50,000 U/kg body weight or amphotericin B oral suspension 25 mg/kg body weight both given daily in 4 doses). Duration: 4 weeks.
Outcomes	Both clinical and mycological assessment of oral candidiasis at 4 weeks, or until remission. Other outcomes: systemic fungal infection, toxicity (adverse events 'probably due to drug').
Notes	

Ninane 1994 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Nucci 2000

Methods	Randomised, parallel group study conducted in Brazil. Patient, provider and assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 4%.
Participants	Adults and children with mixed cancer. 219 patients enrolled and 210 completed.
Interventions	2 groups, placebo versus itraconazole (100 mg capsules every 12 hours at mealtimes). Duration: 3 weeks.
Outcomes	Both clinical and mycological assessment of oral candidiasis at 3 weeks. Other outcomes: systemic fungal infection, death associated with fungal infection, empirical antifungal treatment, toxicity (adverse events 'probably due to drug'), compliance.
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Orlandi 1986

Methods	Randomised, parallel group study conducted in Italy. Patient and provider not blinded, unclear if assessor blinded. Clear information on withdrawals. Unclear whether dentist was involved in the study. Drop outs: 40%.
Participants	Adults with blood cancer. 30 patients enrolled and 18 completed.
Interventions	2 groups, control = no treatment versus amphotericin B (500 mg tablets slowly chewed). Duration: until remission of cancer.
Outcomes	Both clinical and mycological assessment of oral candidiasis. Other outcomes: none.
Notes	Translated from Italian. If temperature gave antibiotics cefalosporine and gentamicina, all patients had corticosteroids.

Risk of bias		
Item	**Authors' judgement**	**Description**

Orlandi 1986 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Owens 1984

Methods	Randomised, parallel group study conducted in USA. Patient, provider and assessor blinded. Unclear information on reasons for withdrawals. Dentist not involved in the study. Drop outs: 81%.
Participants	Adults with mixed cancer. 84 patients enrolled 16 completed.
Interventions	2 groups, placebo versus clotrimazole (10 mg 3 times daily dissolved in mouth). Duration: leukaemia mean = 27 days, neoplasm mean = 37 days.
Outcomes	Both clinical and mycological assessment of oral candidiasis at 4 weeks. Other outcomes: systemic fungal infection, empirical antifungal treatment, toxicity (adverse events 'probably due to drug').
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Palmblad 1992

Methods	Randomised, parallel group study conducted in Sweden. Patient, provider and assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 8%.
Participants	Adults with blood cancer. 116 newly diagnosed patients enrolled and 107 completed.
Interventions	2 groups, placebo versus ketoconazole (200 mg daily). Duration: continued until complete remission diagnosed, blood granulocyte level up, patient discharged or died.
Outcomes	Both clinical and mycological assessment of oral candidiasis. Other outcomes: systemic fungal infection, death associated with fungal infection.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Philpott-Howard 1993

Methods	Randomised, parallel group multicentre study conducted in Europe. Patient, provider and outcome assessor not blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 5%.
Participants	Adults and children with mixed cancer. 536 eligible, 536 enrolled and 511 completed.
Interventions	2 groups, fluconazole (50 mg per day) versus polyenes (nystatin or amphotericin B) (4x10E6 units, 2 g doses per day). Treatment began before chemo/radio. Duration: continued until neutrophil count > 10E9/L, usually 4 weeks, 12 weeks maximum.
Outcomes	Both clinical and mycological assessment of oral candidiasis at 4 weeks, or when neutrophil count was >1x10E9/l, maximum 12 weeks. Other outcomes: systemic fungal infection, toxicity (adverse events 'probably due to drug').
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Rozenberg-Arska 1991

Methods	Randomised, parallel group study conducted in Holland. Patient, provider and assessor of clinical outcome not blinded, assessor of mycological outcome blinded (c). Unclear information on reasons for withdrawal. Dentist not involved in the study. Drop outs: 7%.
Participants	Adults with blood cancer. 54 patients enrolled, 50 completed.
Interventions	2 groups, fluconazole (50 mg 1 dose daily) versus amphotericin B (200 mg in suspension and 200 mg in tablets, 4 times per day). Duration: period of granulocytopenia, 19/20 days.
Outcomes	Both clinical and mycological at 3 weeks. Other outcomes: systemic fungal infection, empirical antifungal treatment, toxicity (adverse events 'probably due to drug').
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Scrimgeour 1985

Methods	Randomised, parallel group study conducted in South Africa. Unclear if patient, provider or assessor blinded. Unclear information on reasons for withdrawal. Dentist not involved in the study. Drop outs: 30%.
Participants	Unclear whether adults or children, with solid cancer. 43 enrolled, 30 completed.
Interventions	2 groups, ketoconazole 200 mg versus ketoconazole 400 mg daily. Duration: unclear.
Outcomes	Both clinical and mycological assessment of oral candidiasis weekly. Other outcomes: toxicity (adverse events 'probably due to drug').
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Vogler 1987

Methods	Randomised, parallel group study conducted in USA. Patient and provider not blinded, unclear if assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 10%.
Participants	Adults with blood cancer. 51 eligible patients and 46 completed.
Interventions	2 groups, ketoconazole (200 mg twice daily) versus nystatin oral suspension (500,000 units 4 times daily). Duration: until absolute granulocyte count was > 1500/ul for 2 days.
Outcomes	Both clinical and mycological assessment of oral candidiasis. Other outcomes: systemic fungal infection, toxicity (adverse events 'probably due to drug').
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Wahlin 1989

Methods	Randomised, parallel group study conducted in Sweden. Patient, provider not blinded, but assessor blinded. Clear information on withdrawals. Dentist involved in the study. Drop outs: 0%.
Participants	Adults and children with blood cancer. 28 patients enrolled and 28 completed.

Wahlin 1989 (*Continued*)

Interventions	2 groups control = no treatment versus chlorhexidine (10 ml of 0.2% chlorhexidine digluconate solution) , twice daily. Duration: 21 days.
Outcomes	Both clinical and mycological assessment of oral candidiasis. Other outcomes: none.
Notes	First episode data for each patient used.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Williams 1977

Methods	Randomised, parallel group study conducted in UK. Patient, provider and assessor not blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 0%.
Participants	Adults and children with blood cancer. 56 patients eligible, enrolled and completed.
Interventions	3 groups control = no treatment versus nystatin (100,000 units in 10 ml of methylcellulose), natamycin (10 ml of 0.25% suspension) both every 2 hours. Duration: 50 days.
Outcomes	Clinical assessment of oral candidiasis at 7 weeks. Other outcomes: none.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Winston 1993

Methods	Randomised, parallel group multicentre study conducted in USA. Patient, provider and assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: < 1%.
Participants	Adults with blood cancer. 257 enrolled and 255 completed.
Interventions	2 groups, placebo versus fluconazole capsule (100 mg 4 times daily or administered intravenously - 200 mg every 12 hours, infused over 1 hour). Duration: through course of chemo until change of neutrophil count reached 1000 cells per mm, maximum 10 weeks.

Winston 1993 (*Continued*)

Outcomes	Mycological assessment of oral candidiasis at 10 weeks. Other outcomes: systemic fungal infection, empirical antifungal treatment, toxicity (adverse events 'probably due to drug'). (Death was reported however it was unclear whether this was associated with a fungal infection.)
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Yamada 1993

Methods	Randomised, parallel group study conducted in Japan. Patient and provider not blinded, unclear if assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 2%.
Participants	Adults with blood cancer. 111 patients enrolled, 109 completed.
Interventions	2 groups control = no treatment versus norofloxacin (200 mg orally 2 or 4 times daily). Duration: 4 weeks or until neutrophil count was > 1000/uL.
Outcomes	Clinical assessment of oral candidiasis at 4 weeks or until neutrophil count was > 1000/uL. Other outcomes: systemic fungal infection.
Notes	Called "stomatitis".

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Yeo 1985

Methods	Randomised, parallel group study conducted in USA. Patient, provider not blinded, but assessor blinded. Unclear information on reasons for withdrawal. Dentist not involved in the study. Drop outs: 32%.
Participants	Adults with mixed cancer. 296 patients enrolled and 202 completed
Interventions	2 groups control = no treatment versus clotrimazole (10 mg troche 3 times daily - dissolve over 15 to 20 minutes). Duration: 8 weeks.
Outcomes	Both clinical and mycological assessment of oral candidiasis at 8 weeks. Other outcomes: none.

Yeo 1985 (*Continued*)

Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

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

Akiyama 1993	Episodes not patients.
Annaloro 1995	No useable outcome.
Biancofiore 2002	Liver transplant patients (liposomal, amphotericin B + itraconazole versus fluconazole + itraconazole).
Bodey 1994a	No oral outcome.
Bodey 1994b	Used as an empirical therapy only treating patients with documented infection. Episodes not patients (antibiotic therapy versus +/- GM-CFS).
Boogaerts 2001	No suitable outcomes (itraconazole versus amphotericin B + nystatin).
Brammer 1990	No oral outcome.
Cagnoni 2000	No useable outcomes (liposomal amphotericin B versus conventional amphotericin B).
Cagnoni 2002	Same study as Walsh 1999 but no suitable outcomes.
Charak 1988	Not randomised although described as such (odd or even days of month). Episodes not patients (clotrimazole versus nystatin).
Ellis 1994	No oral outcome.
EORTC 1989	Used as an empirical therapy only treating patients with infection (amphotericin B versus no treatment).
Epstein 1996	Not RCT (fluconazole).
Epstein 2004	Inappropriate study design, some patients had oral candidiasis pre-treatment - not prophylaxis (amphotericin B verus nystatin).
Ezdinli 1971	Inappropriate study design: autopsy study (amphotericin B versus placebo).
Finke 1990	No oral outcome.
Gava 1996	Episodes not patients.
Glasmacher 2006	Invasive fungal infection, no suitable outcomes (itraconazole versus fluconazole).
Goranov 1999	Not RCT (fluconazole versus no treatment).
Gozdasoglu 1999	Not RCT (none).
Gualtieri 1983	No oral outcome.
Gurwith 1979	No oral outcome.

(*Continued*)

Hansen 1987	Episodes not patients.
Harousseau 1998	Abstract, insufficient information (itraconazole oral solution versus amphotericin B capsules).
Harousseau 2000	No oral outcome.
Hiemenz 2005	Interventions for systemic candidiasis not oral (micafungin + fluconazole versus fluconazole).
Hoppe 1995	No oral outcome.
Jones 1984	No useable data.
Kaptan 2003	Episodes not patients (itraconazole versus no treatment).
Kelsey 1999	No suitable outcome as cannot separate superficial and systemic outcomes (amBisome versus placebo).
Kern 1991	No oral outcome.
Koc 2003	The outcome presented was symptomatic clinical candidiasis with grade 3 to 4 mucositis and oral microbiological assessments confirming yeast. This outcome was not consistent with those for this review.
Lass-Florl 2003	Colonisation prior to entry into the study.
Laverdiere 2000	No oral outcome.
Malcolm 1982	Abstract, insufficient information.
Malik 1998	Used as an empirical therapy only treating patients with documented infection (fluconazole versus amphotericin B).
Marr 2004	No oral outcomes given (cyclophosphamide).
Marr 2004b	Primary outcome "invasive mould infections" and no oral outcomes mentioned (itraconazole).
Mattiuzzi 2003	No suitable outcome - proven fungal infection but do not know if it is oral (itraconazole versus amphotericin B).
Mattiuzzi 2006	Interventions for systemic candidiasis not oral (itraconazole versus caspofungin).
Meunier 1989	Episodes not patients, patients re-randomised into study.
Meunier 1991	Episodes not patients.
Meunier-C 1983	No oral outcome.
Milliken 1989	Abstract, insufficient information.
Mitrokhin 2003	Not RCT (Russian) (itraconazole).

(*Continued*)

Morgenstern 1999	Episodes not patients (itraconazole versus fluconazole).
Mucke 1997	Not RCT.
Nicolatou 2003	Not RCT, confirmed by authors (amifostine).
Nicolatou 2006	Not RCT.
Noguchi 2000	Unclear if RCT or not (written to author, but no reply).
Nomura 2006	Not RCT (cost effectiveness).
Paiva 1994	Not RCT (Portuguese - translated) (fluconazole).
Peterson 1984	No suitable outcomes (tobramycin and ticarcillin for either 3 days or until no longer glanulocytopenic).
Prentice 1989	Not RCT (itraconazole).
Priour 1995	No suitable outcome, (compliance not disease).
Ringden 2002	Not RCT (amphotericin B).
Rotstein 1999	No oral outcome.
Schaffner 1995	Episodes not patients.
Schaison 1990	No suitable outcome (teicoplanin versus fluconazole).
Shepp 1985	Data in wrong form (not patient based).
Silling 1998	Used as an empirical therapy only treating patients with infection (fluconazole versus amphotericin B).
Silling 1999	Same as Silling 1988 but in French (fluconazole versus amphotericin B).
Sleijfer 1980	Episodes not patients.
Subira 2004b	Not prophylaxis as treatment of fever.
Timmers 2000	Study halted early due to toxic effect of amphotericin B colloidal dispersion (amphocil) (fluconazole versus amphotericin B).
Tollemar 1994	Abstract of 2 RCTs, with insufficient data to include (AmBisome).
Turhan 1987	No oral outcome.
Urabe 1990	Not RCT.

(*Continued*)

Van't Wout 1991	Not RCT (German) (amphotericin B versus itraconazole).
Vehreschild 2007	Candidiasis is not a primary outcome.
Vreugdenhil 1993	No oral outcome.
Walsh 1991	Used as an empirical therapy only treating patients with infection (amphotericin versus ketoconazole).
Walsh 2002a	Used as an empirical therapy only treating patients with infection (voriconazole versus amphotericin B).
Walsh 2002b	Not RCT.
Walsh 2004	Empirical therapy only treating patients with infection (voriconazole versus ketoconazole).
Wang 2003	Unsure if RCT, and outcome is not oral.
Weiser 1981	Episodes not patients.
Winston 2000	Used as an empirical therapy only treating patients with infection. No suitable outcome (fluconazole versus amphotericin B).
Wolff 2000	No suitable outcomes (fluconazole versus amphotericin B).
Yamac 1995	No suitable outcomes (fluconazole versus no treatment control).
Young 1999	Repeat enrolment of patients, which included people with oropharyngeal culture at entry.
Zacharof 1999	Abstract - insufficient information to include.

RCT = randomised controlled trial

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

Corvo 2008

Methods	Randomised, parallel group study conducted in 20 sites in Italy. Patient, provider and assessor blinded. Clear information on withdrawals. Dentist not involved in the study. Drop outs: 35%.
Participants	Adults with solid cancer. 270 randomised (138 fluconazole, 132 placebo; 2 did not have post baseline data) 43 and 52 discontinued in fluconazole and placebo groups respectively with reasons given.
Interventions	2 groups control = placebo versus fluconazole (100 mg) once daily from sixth to last session of radiotherapy . Duration: maximum of 56 days.

Corvo 2008 (*Continued*)

Outcomes	Mycologic assessment of oral cavity every 2 weeks and at end by direct microscopic evaluation and culture for search of Candida. Other outcomes: days to outbreak (Kaplan Meier survival curve). RTOG acute toxicity score, adverse events.
Notes	

Elad 2006

Methods	Randomised, parallel group study conducted in Israel. Patient and provider not blinded; unclear if assessor blinded. Clear information on withdrawals. Dentist not involved in the study.
Participants	Adults with mixed cancer. 20 patients enrolled and completed.
Interventions	2 groups chlorhexidine (0.2% mouthrinse x4/day) versus chlorhexidine (0.2% mouthrinse x4/day) with amphotericin B (10mg lozenges x4/day). Duration: 7 days prior to HSCT until discharge from hospital (on average about 50 days).
Outcomes	Clinical assessment of oral candidiasis twice weekly basis from day -7 until one month after discharge. Other outcomes: hospitalisation, medication.
Notes	

RTOG = Radiation Therapy Oncology Group
HSCT = hematopoietic stem cell transplantation

DATA AND ANALYSES

Comparison 1. Comparisons with placebo/no treatment for all drug types

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral candidiasis present	18		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 drugs absorbed from GI tract	7	1153	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.78]
1.2 drugs partially absorbed from GI tract	4	292	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.06, 0.46]
1.3 drugs not absorbed from GI tract	8	382	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.47, 1.01]
2 Systemic fungal infection	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 drugs absorbed from GI tract	6	1041	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.37, 1.14]
2.2 drugs partially absorbed from GI tract	1	32	Risk Ratio (M-H, Random, 95% CI)	2.27 [0.23, 22.56]
2.3 drugs not absorbed from GI tract	2	71	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 1.75]
3 Death	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 drugs absorbed from GI tract	3	718	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.14, 15.43]
3.2 drugs partially absorbed from GI tract	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 drugs not absorbed from GI tract	1	51	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.01, 2.95]
4 Empirical antifungal treatment	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 drugs absorbed from GI tract	2	465	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.73, 0.99]
4.2 drugs partially absorbed for GI tract	1	32	Risk Ratio (M-H, Random, 95% CI)	3.38 [0.15, 77.12]
4.3 drugs not absorbed from GI tract	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5 Toxicity (adverse events 'probably due to drug')	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 drugs absorbed from GI tract	3	871	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.84, 1.67]
5.2 drugs partially absorbed from GI tract	2	60	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.3 drugs not absorbed from GI tract	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6 Good compliance	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 drugs absorbed from GI tract	2	615	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.89, 1.27]

Comparison 2. Comparisons between drugs absorbed from GI tract and those not absorbed

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral candidiasis present	8	2103	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.76]
2 Systemic fungal infection	8	2103	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.33, 1.06]
3 Death	3	981	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.38, 4.13]
4 Empirical antifungal treatment	4	1031	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.68, 1.16]
5 Toxicity (adverse events 'probably due to drug')	6	2018	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.33, 2.30]
6 Good compliance	1	820	Risk Ratio (M-H, Random, 95% CI)	1.05 [1.03, 1.08]

Comparison 3. Comparison of drugs absorbed from the GI tract

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral candidiasis present	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Itraconazole versus fluconazole	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Ketoconazole versus itraconazole	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Ketoconazole (400 mg) versus ketoconazole (200 mg)	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Systemic fungal infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Intraconazole versus fluconazole	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Itraconazole versus fluconazole	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Empirical antifungal treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Itraconazole versus fluconazole	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
5 Toxicity (adverse events 'probably due to drug')	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Itraconazole versus fluconazole	2		Risk Ratio (M-H, Random, 95% CI)	Not estimable
6 Good compliance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Itraconazole versus fluconazole	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 4. Comparison of drugs not absorbed from GI tract

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral candidiasis present	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Chlorhexidine versus nystatin	1	34	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.36, 2.21]
1.2 Chlorhexidine versus chlorhexidine plus nystatin	1	52	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.64, 4.10]
1.3 Nystatin versus chlorhexidine plus nystatin	1	50	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.73, 4.54]
1.4 Nystatin versus natamycin	1	28	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.83, 1.37]
1.5 Norfloxacin + amphotericin B versus amphotericin B	1	106	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.15, 1.00]

Comparison 5. Comparisons with placebo/no treatment for not absorbed drug types

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral candidiasis present	8	351	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.54, 1.07]
1.1 Nystatin	3	153	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.08]
1.2 Amphotericin B	2	48	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.18, 1.23]
1.3 Chlorhexidine	3	115	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.19, 1.83]
1.4 Thymostimulin	1	35	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.12, 1.32]

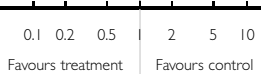
Analysis 1.1. Comparison 1 Comparisons with placebo/no treatment for all drug types, Outcome 1 Oral candidiasis present.

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

Comparison: 1 Comparisons with placebo/no treatment for all drug types

Outcome: 1 Oral candidiasis present

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 drugs absorbed from GI tract					
Bodey 1990	1/58	15/54		8.3 %	0.06 [0.01, 0.45]
Brincker 1983	2/19	8/19		12.1 %	0.25 [0.06, 1.03]
Caselli 1990	7/20	6/10		18.0 %	0.58 [0.27, 1.28]
Menichetti 1999	10/201	11/204		17.5 %	0.92 [0.40, 2.12]
Nucci 2000	1/104	6/106		7.8 %	0.17 [0.02, 1.39]
Palmblad 1992	12/50	19/53		19.6 %	0.67 [0.36, 1.23]
Winston 1993	6/123	16/132		16.8 %	0.40 [0.16, 1.00]
Subtotal (95% CI)	**575**	**578**		**100.0 %**	**0.47 [0.29, 0.78]**
Total events: 39 (Treatment), 81 (Control)					
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 10.18$, df = 6 (P = 0.12); $I^2 = 41\%$					
Test for overall effect: Z = 2.91 (P = 0.0036)					
2 drugs partially absorbed from GI tract					
Brincker 1978	2/15	7/15		27.6 %	0.29 [0.07, 1.16]
Cuttner 1986	1/16	8/12		19.4 %	0.09 [0.01, 0.65]
Owens 1984	3/15	11/17		34.1 %	0.31 [0.11, 0.90]
Yeo 1985	1/101	27/101		18.9 %	0.04 [0.01, 0.27]
Subtotal (95% CI)	**147**	**145**		**100.0 %**	**0.16 [0.06, 0.46]**
Total events: 7 (Treatment), 53 (Control)					
Heterogeneity: $Tau^2 = 0.46$; $Chi^2 = 5.31$, df = 3 (P = 0.15); $I^2 = 44\%$					
Test for overall effect: Z = 3.48 (P = 0.00051)					
3 drugs not absorbed from GI tract					
Buchanan 1985	24/39	26/39		16.1 %	0.92 [0.66, 1.29]
Caselli 1990	4/10	6/10		12.3 %	0.67 [0.27, 1.66]
Epstein 1992	19/68	5/18		12.9 %	1.01 [0.44, 2.32]
Ferretti 1988	2/24	15/27		9.2 %	0.15 [0.04, 0.59]
Giorgis 1991	3/18	7/17		10.5 %	0.40 [0.12, 1.32]
Orlandi 1986	2/15	7/13		9.1 %	0.25 [0.06, 0.99]



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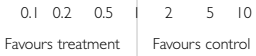
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Wahlin 1989	6/14	7/14		13.2 %	0.86 [0.39, 1.91]
Williams 1977	25/28	28/28		16.7 %	0.89 [0.78, 1.03]
Subtotal (95% CI)	**216**	**166**		**100.0 %**	**0.69 [0.47, 1.01]**
Total events: 85 (Treatment), 101 (Control)					
Heterogeneity: Tau² = 0.14; Chi² = 20.91, df = 7 (P = 0.004); I² =67%					
Test for overall effect: Z = 1.89 (P = 0.058)					



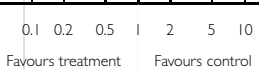
Analysis 1.2. Comparison 1 Comparisons with placebo/no treatment for all drug types, Outcome 2 Systemic fungal infection.

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

Comparison: 1 Comparisons with placebo/no treatment for all drug types

Outcome: 2 Systemic fungal infection

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 drugs absorbed from GI tract				
Brincker 1983	2/19	2/19		1.00 [0.16, 6.38]
Caselli 1990	0/20	0/10		0.0 [0.0, 0.0]
Menichetti 1999	5/201	9/204		0.56 [0.19, 1.65]
Nucci 2000	5/104	9/106		0.57 [0.20, 1.63]
Palmblad 1992	3/50	0/53		7.41 [0.39, 139.97]
Winston 1993	5/123	10/132		0.54 [0.19, 1.53]
Subtotal (95% CI)	**517**	**524**		**0.65 [0.37, 1.14]**
Total events: 20 (Treatment), 30 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 3.17, df = 4 (P = 0.53); I² =0.0%				
Test for overall effect: Z = 1.50 (P = 0.13)				
2 drugs partially absorbed from GI tract				
Owens 1984	2/15	1/17		2.27 [0.23, 22.56]
Subtotal (95% CI)	**15**	**17**		**2.27 [0.23, 22.56]**
Total events: 2 (Treatment), 1 (Control)				



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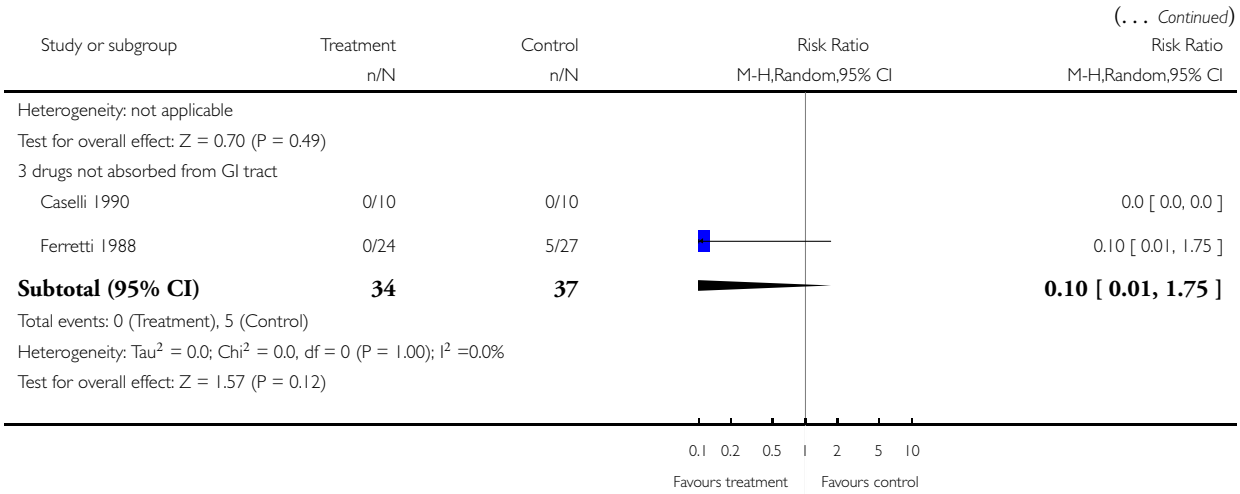
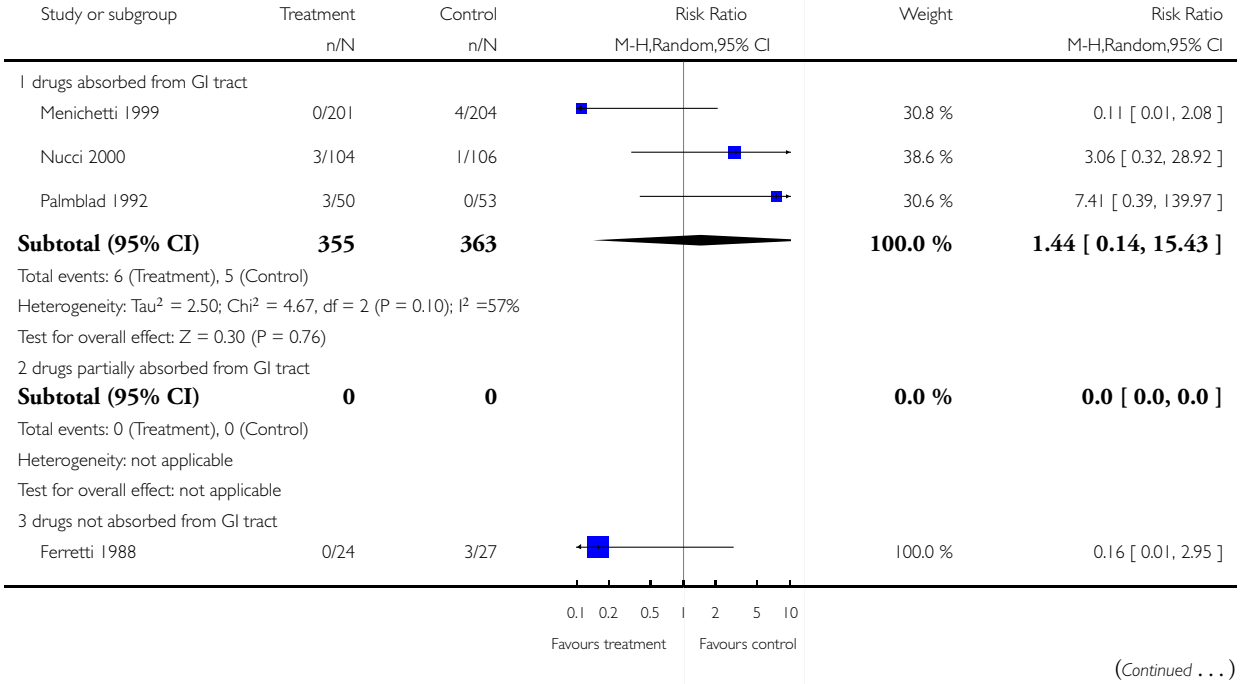


Analysis 1.3. Comparison 1 Comparisons with placebo/no treatment for all drug types, Outcome 3 Death.

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

Comparison: 1 Comparisons with placebo/no treatment for all drug types

Outcome: 3 Death



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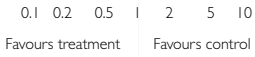
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**24**	**27**		**100.0 %**	**0.16 [0.01, 2.95]**
Total events: 0 (Treatment), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.23 (P = 0.22)					



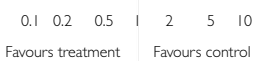
Analysis 1.4. Comparison 1 Comparisons with placebo/no treatment for all drug types, Outcome 4 Empirical antifungal treatment.

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

Comparison: 1 Comparisons with placebo/no treatment for all drug types

Outcome: 4 Empirical antifungal treatment

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 drugs absorbed from GI tract					
Nucci 2000	26/104	36/106		13.2 %	0.74 [0.48, 1.13]
Winston 1993	79/123	98/132		86.8 %	0.87 [0.73, 1.02]
Subtotal (95% CI)	**227**	**238**		**100.0 %**	**0.85 [0.73, 0.99]**
Total events: 105 (Treatment), 134 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.55, df = 1 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 2.11 (P = 0.035)					
2 drugs partially absorbed for GI tract					
Owens 1984	1/15	0/17		100.0 %	3.38 [0.15, 77.12]
Subtotal (95% CI)	**15**	**17**		**100.0 %**	**3.38 [0.15, 77.12]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					
3 drugs not absorbed from GI tract					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



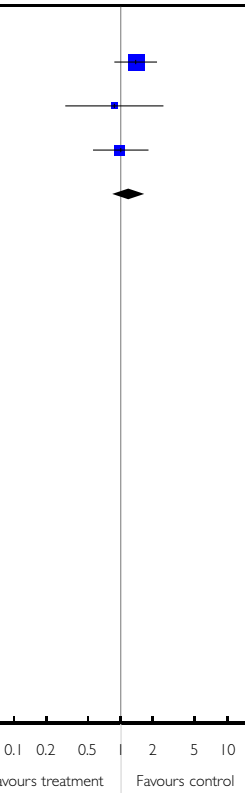
Analysis 1.5. Comparison 1 Comparisons with placebo/no treatment for all drug types, Outcome 5 Toxicity (adverse events 'probably due to drug').

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

Comparison: 1 Comparisons with placebo/no treatment for all drug types

Outcome: 5 Toxicity (adverse events 'probably due to drug')

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 drugs absorbed from GI tract				
Menichetti 1999	37/201	27/204		1.39 [0.88, 2.19]
Nucci 2000	6/104	7/106		0.87 [0.30, 2.51]
Winston 1993	19/132	18/124		0.99 [0.55, 1.80]
Subtotal (95% CI)	**437**	**434**		**1.18 [0.84, 1.67]**
Total events: 62 (Treatment), 52 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.14$, df = 2 (P = 0.57); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.97 (P = 0.33)				
2 drugs partially absorbed from GI tract				
Cuttner 1986	0/16	0/12		0.0 [0.0, 0.0]
Owens 1984	0/15	0/17		0.0 [0.0, 0.0]
Subtotal (95% CI)	**31**	**29**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P<0.00001); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 drugs not absorbed from GI tract				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				



Analysis 1.6. Comparison 1 Comparisons with placebo/no treatment for all drug types, Outcome 6 Good compliance.

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

Comparison: 1 Comparisons with placebo/no treatment for all drug types

Outcome: 6 Good compliance

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 drugs absorbed from GI tract					
Menichetti 1999	167/201	147/204		47.8 %	1.15 [1.04, 1.28]
Nucci 2000	96/104	99/106		52.2 %	0.99 [0.92, 1.07]

Analysis 2.1. Comparison 2 Comparisons between drugs absorbed from GI tract and those not absorbed, Outcome 1 Oral candidiasis present.

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

Comparison: 2 Comparisons between drugs absorbed from GI tract and those not absorbed

Outcome: 1 Oral candidiasis present

Study or subgroup	Favours absorbed n/N	Favours non-absorbed n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Caselli 1990	7/20	4/10		0.88 [0.33, 2.30]
Egger 1995	0/43	0/46		0.0 [0.0, 0.0]
Hann 1982	6/37	27/35		0.21 [0.10, 0.45]
Menichetti 1994	7/420	10/400		0.67 [0.26, 1.73]
Ninane 1994	3/236	15/249		0.21 [0.06, 0.72]
Philpott-Howard 1993	4/256	22/255		0.18 [0.06, 0.52]
Rozenberg-Arska 1991	0/25	1/25		0.33 [0.01, 7.81]
Vogler 1987	3/22	2/24		1.64 [0.30, 8.90]
Total (95% CI)	**1059**	**1044**		**0.40 [0.21, 0.76]**

Total events: 30 (Favours absorbed), 81 (Favours non-absorbed)

Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 12.47$, df = 6 (P = 0.05); $I^2 = 52\%$

Test for overall effect: Z = 2.83 (P = 0.0047)

Analysis 2.2. Comparison 2 Comparisons between drugs absorbed from GI tract and those not absorbed, Outcome 2 Systemic fungal infection.

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

Comparison: 2 Comparisons between drugs absorbed from GI tract and those not absorbed

Outcome: 2 Systemic fungal infection

Study or subgroup	Favours absorbed n/N	Favours non-absorbed n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Caselli 1990	0/20	0/10		0.0 [0.0, 0.0]
Egger 1995	1/43	2/46		0.53 [0.05, 5.69]
Hann 1982	2/37	16/35		0.12 [0.03, 0.48]
Menichetti 1994	11/420	10/400		1.05 [0.45, 2.44]
Ninane 1994	2/236	5/249		0.42 [0.08, 2.15]
Philpott-Howard 1993	6/256	9/255		0.66 [0.24, 1.84]
Rozenberg-Arska 1991	1/25	0/25		3.00 [0.13, 70.30]
Vogler 1987	5/22	8/24		0.68 [0.26, 1.77]
Total (95% CI)	**1059**	**1044**		**0.59 [0.33, 1.06]**

Total events: 28 (Favours absorbed), 50 (Favours non-absorbed)

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 8.34$, df = 6 (P = 0.21); $I^2 = 28\%$

Test for overall effect: Z = 1.76 (P = 0.078)

Analysis 2.3. Comparison 2 Comparisons between drugs absorbed from GI tract and those not absorbed, Outcome 3 Death.

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

Comparison: 2 Comparisons between drugs absorbed from GI tract and those not absorbed

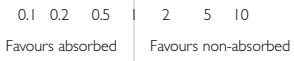
Outcome: 3 Death

Study or subgroup	Favours absorbed n/N	Favours non-absorbed n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Egger 1995	1/43	0/46		14.1 %	3.20 [0.13, 76.60]
Hann 1982	0/37	2/35		15.8 %	0.19 [0.01, 3.81]
Menichetti 1994	5/420	3/400		70.1 %	1.59 [0.38, 6.60]
Total (95% CI)	**500**	**481**		**100.0 %**	**1.25 [0.38, 4.13]**

Total events: 6 (Favours absorbed), 5 (Favours non-absorbed)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.99$, df = 2 (P = 0.37); $I^2 = 0.0\%$

Test for overall effect: Z = 0.37 (P = 0.71)



Analysis 2.4. Comparison 2 Comparisons between drugs absorbed from GI tract and those not absorbed, Outcome 4 Empirical antifungal treatment.

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

Comparison: 2 Comparisons between drugs absorbed from GI tract and those not absorbed

Outcome: 4 Empirical antifungal treatment

Study or subgroup	Favours absorbed n/N	Favours non-absorbed n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Egger 1995	23/43	22/46		35.4 %	1.12 [0.74, 1.69]
Hann 1982	3/37	2/35		2.4 %	1.42 [0.25, 7.99]
Menichetti 1994	67/420	85/400		60.9 %	0.75 [0.56, 1.00]
Rozenberg-Arska 1991	2/25	1/25		1.3 %	2.00 [0.19, 20.67]
Total (95% CI)	**525**	**506**		**100.0 %**	**0.89 [0.68, 1.16]**

Total events: 95 (Favours absorbed), 110 (Favours non-absorbed)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.30$, df = 3 (P = 0.35); $I^2 = 9\%$

Test for overall effect: Z = 0.86 (P = 0.39)

Analysis 2.5. Comparison 2 Comparisons between drugs absorbed from GI tract and those not absorbed, Outcome 5 Toxicity (adverse events 'probably due to drug').

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

Comparison: 2 Comparisons between drugs absorbed from GI tract and those not absorbed

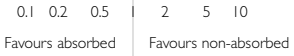
Outcome: 5 Toxicity (adverse events 'probably due to drug')

Study or subgroup	Favours absorbed n/N	Favours non-absorbed n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Egger 1995	1/43	3/46		11.2 %	0.36 [0.04, 3.30]
Menichetti 1994	6/420	28/400		22.5 %	0.20 [0.09, 0.49]
Ninane 1994	38/245	21/257		25.7 %	1.90 [1.15, 3.14]
Philpott-Howard 1993	15/256	14/255		24.0 %	1.07 [0.53, 2.17]
Rozenberg-Arska 1991	3/25	0/25		7.9 %	7.00 [0.38, 128.87]
Vogler 1987	1/22	1/24		8.7 %	1.09 [0.07, 16.41]
Total (95% CI)	**1011**	**1007**		**100.0 %**	**0.88 [0.33, 2.30]**

Total events: 64 (Favours absorbed), 67 (Favours non-absorbed)

Heterogeneity: $Tau^2 = 0.88$; $Chi^2 = 21.78$, df = 5 (P = 0.00058); $I^2 = 77\%$

Test for overall effect: Z = 0.27 (P = 0.79)



Analysis 2.6. Comparison 2 Comparisons between drugs absorbed from GI tract and those not absorbed, Outcome 6 Good compliance.

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

Comparison: 2 Comparisons between drugs absorbed from GI tract and those not absorbed

Outcome: 6 Good compliance

Study or subgroup	Favours absorbed n/N	Favours non-absorbed n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Menichetti 1994	416/420	376/400		100.0 %	1.05 [1.03, 1.08]
Total (95% CI)	**420**	**400**		**100.0 %**	**1.05 [1.03, 1.08]**

Total events: 416 (Favours absorbed), 376 (Favours non-absorbed)

Heterogeneity: not applicable

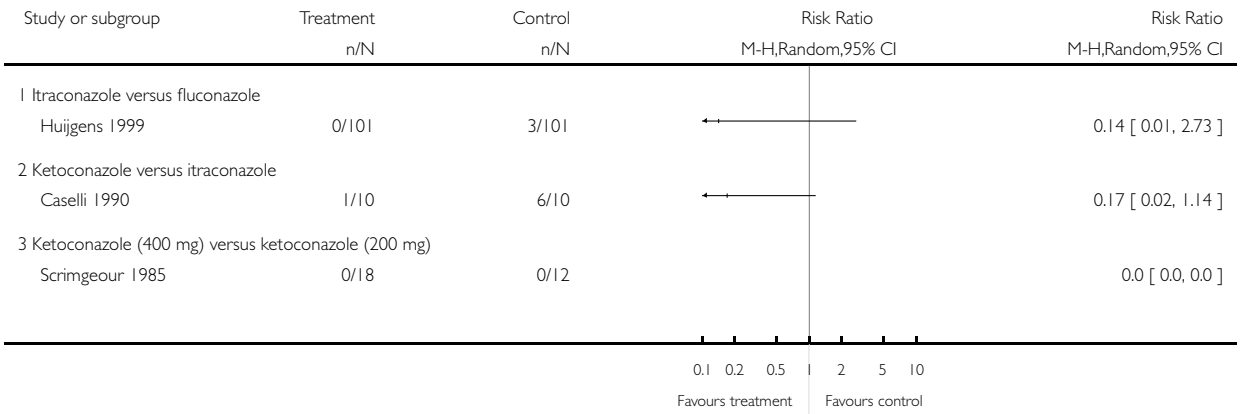
Test for overall effect: Z = 3.87 (P = 0.00011)

Analysis 3.1. Comparison 3 Comparison of drugs absorbed from the GI tract, Outcome 1 Oral candidiasis present.

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

Comparison: 3 Comparison of drugs absorbed from the GI tract

Outcome: 1 Oral candidiasis present

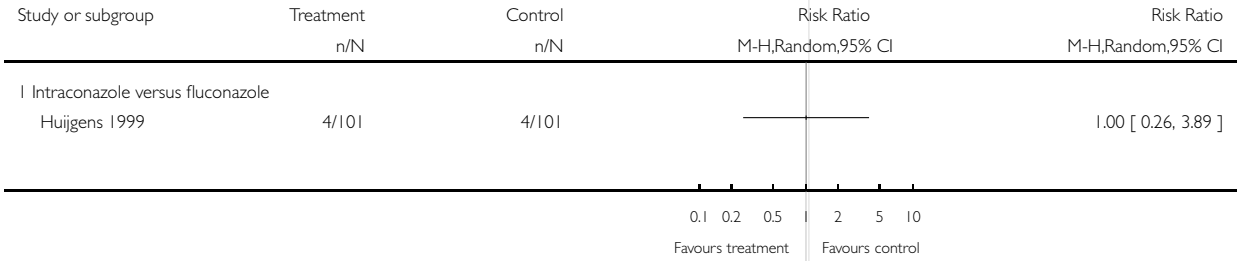


Analysis 3.2. Comparison 3 Comparison of drugs absorbed from the GI tract, Outcome 2 Systemic fungal infection.

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

Comparison: 3 Comparison of drugs absorbed from the GI tract

Outcome: 2 Systemic fungal infection



Analysis 3.3. Comparison 3 Comparison of drugs absorbed from the GI tract, Outcome 3 Death.

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

Comparison: 3 Comparison of drugs absorbed from the GI tract

Outcome: 3 Death

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Itraconazole versus fluconazole				
Huijgens 1999	0/101	3/101		0.14 [0.01, 2.73]

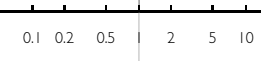
Analysis 3.4. Comparison 3 Comparison of drugs absorbed from the GI tract, Outcome 4 Empirical antifungal treatment.

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

Comparison: 3 Comparison of drugs absorbed from the GI tract

Outcome: 4 Empirical antifungal treatment

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Itraconazole versus fluconazole				
Huijgens 1999	1/101	2/101		0.50 [0.05, 5.43]



Analysis 3.5. Comparison 3 Comparison of drugs absorbed from the GI tract, Outcome 5 Toxicity (adverse events 'probably due to drug').

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

Comparison: 3 Comparison of drugs absorbed from the GI tract

Outcome: 5 Toxicity (adverse events 'probably due to drug')

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Itraconazole versus fluconazole				
Huijgens 1999	0/101	0/101		0.0 [0.0, 0.0]
Scrimgeour 1985	0/12	0/18		0.0 [0.0, 0.0]

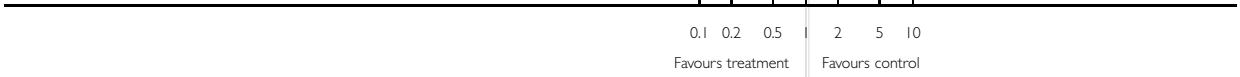
Analysis 3.6. Comparison 3 Comparison of drugs absorbed from the GI tract, Outcome 6 Good compliance.

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

Comparison: 3 Comparison of drugs absorbed from the GI tract

Outcome: 6 Good compliance

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Itraconazole versus fluconazole				
Huijgens 1999	86/101	91/101		0.95 [0.85, 1.05]

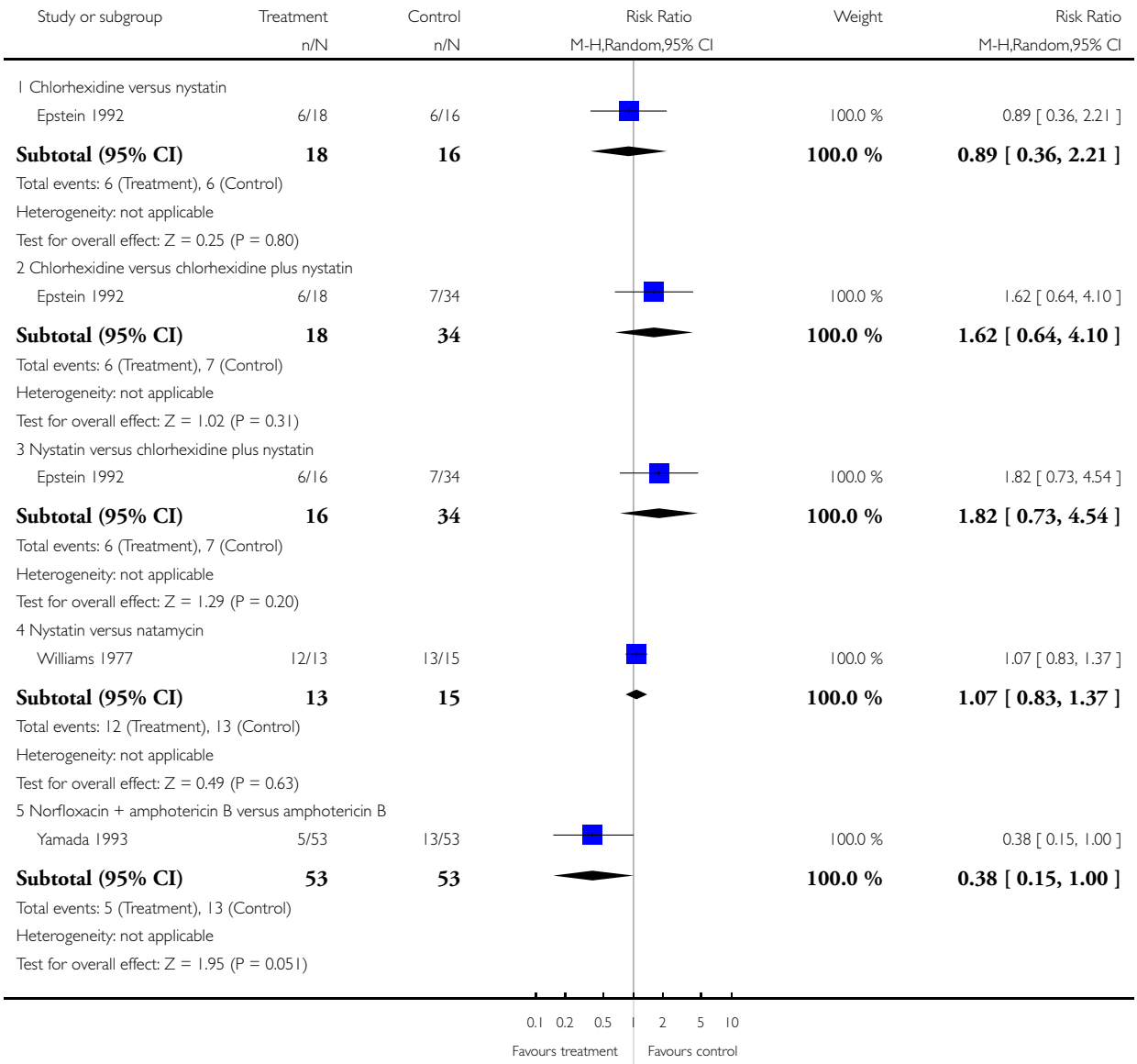


Analysis 4.1. Comparison 4 Comparison of drugs not absorbed from GI tract, Outcome 1 Oral candidiasis present.

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

Comparison: 4 Comparison of drugs not absorbed from GI tract

Outcome: 1 Oral candidiasis present

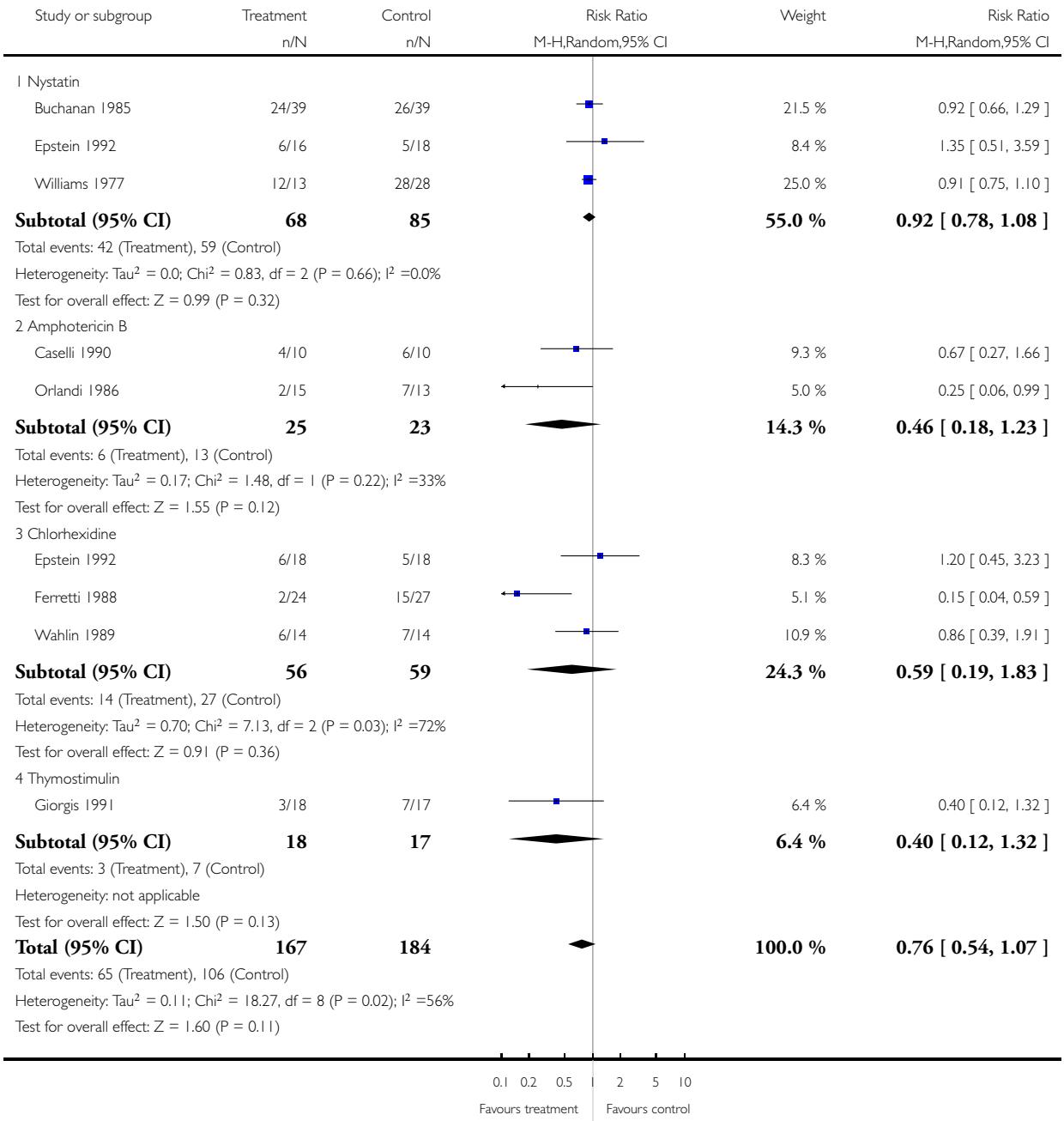


Analysis 5.1. Comparison 5 Comparisons with placebo/no treatment for not absorbed drug types, Outcome 1 Oral candidiasis present.

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

Comparison: 5 Comparisons with placebo/no treatment for not absorbed drug types

Outcome: 1 Oral candidiasis present



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

11. 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

Cochrane / OHG Search filter for MEDLINE via OVID

Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (September 2008 revision) as referenced in Chapter 6 and detailed in box 6.4.c of The Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [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 SS 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. 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 use with 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

Appendix 6. 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 7. SIGLE search strategy

N.B. SIGLE is now provided through OpenSIGLE: http://opensigle.inist.fr/

SIGLE no longer supports complex searching, so a series of keyword searches was performed as below:
cancer AND mucositis AND oral
leukemia AND mucositis AND oral
leukaemia AND mucositis AND oral
carcinoma AND mucositis AND oral
lymphoma AND mucositis AND oral
tumour AND mucositis AND oral
tumor AND mucositis AND oral
cancer AND candidiasis AND oral
leukemia AND candidiasis AND oral
leukaemia AND candidiasis AND oral
carcinoma AND candidiasis AND oral
lymphoma AND candidiasis AND oral
tumour AND candidiasis AND oral
tumor AND candidiasis AND oral

Appendix 8. 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$) OR (Tw oral AND Tw candidiasis$)

WHAT'S NEW

Last assessed as up-to-date: 4 August 2009.

5 August 2009	New search has been performed	Search re-run and 2 studies identified which have been added as pending. Neither study will change the results or conclusions of the review. In one study Elad 2006 - no patients got candidiasis. Corvo 2008 fluconazole is compared to placebo, showing a reduction in candidiasis. This will not change the conclusions of the review. One excluded study Vehreschild 2007 added.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 2000

7 November 2006	New citation required but conclusions have not changed	With this update we found no new included trials but new excluded studies. This makes no difference to the results or to the conclusions.

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

None known.

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INDEX TERMS

Medical Subject Headings (MeSH)

Antifungal Agents [pharmacokinetics; *therapeutic use]; Candidiasis, Oral [*prevention & control]; Intestinal Absorption; Neoplasms [*drug therapy; *radiotherapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans