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

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TABLE OF CONTENTS

[Intervention Review]

Interventions for treating oral candidiasis for patients with cancer receiving treatment

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ABSTRACT

Background

Treatment of cancer is increasingly effective but is associated with short and long term side effects. Oral and gastrointestinal side effects, including oral candidiasis, remain a major source of illness despite the use of a variety of agents to treat them.

Objectives

To assess the effectiveness of interventions for the treatment of oral candidiasis for patients with cancer receiving chemotherapy or radiotherapy or both.

Search methods

Computerised searches of Cochrane Oral Health Group and PaPaS Trials Registers (to 1 June 2010), CENTRAL via *the Cochrane Library* (Issue 2, 2010, 1 June 2010), MEDLINE via OVID (1 June 2010), EMBASE via OVID (1 June 2010), CINAHL via EBSCO (1 June 2010), CANCERLIT via PubMed (1 June 2010), OpenSIGLE (1 June 2010) and LILACS via Virtual Health Library (1 June 2010) were undertaken.
Reference lists from relevant articles were searched and the authors of eligible trials were contacted to identify trials and obtain additional information.

Selection criteria

All randomised controlled trials comparing agents prescribed to treat oral candidiasis in people receiving chemotherapy or radiotherapy for cancer. The outcomes were eradication of oral candidiasis, dysphagia, systemic infection, amount of analgesia, length of hospitalisation, cost and patient quality of life.

Data collection and analysis

Data were independently extracted, in duplicate, by two review authors. Trial authors were contacted for details of randomisation and withdrawals and a quality assessment was carried out. Risk ratios (RR) were calculated using fixed-effect models.

Main results

Ten trials involving 940 patients, satisfied the inclusion criteria and are included in this review. Drugs absorbed from the gastrointestinal (GI) tract were beneficial in eradication of oral candidiasis compared with drugs not absorbed from the GI tract (three trials: RR = 1.29, 95%

confidence interval (CI) 1.09 to 1.52), however there was significant heterogeneity. A drug absorbed from the GI tract, ketoconazole, was more beneficial than placebo in eradicating oral candidiasis (one trial: RR = 3.61, 95% CI 1.47 to 8.88). Clotrimazole, at a higher dose of 50 mg was more effective than a lower 10 mg dose in eradicating oral candidiasis, when assessed mycologically (one trial: RR = 2.00, 95% CI 1.11 to 3.60). Only one of the ten trials was assessed as at low risk of bias.

Authors' conclusions

There is insufficient evidence to claim or refute a benefit for any antifungal agent in treating candidiasis. Further well designed, placebo-controlled trials assessing the effectiveness of old and new interventions for treating oral candidiasis are needed. Clinicians need to make a decision on whether to prevent or treat oral candidiasis in patients receiving treatment for cancer.

PLAIN LANGUAGE SUMMARY

Interventions for treating oral candidiasis for patients with cancer receiving treatment

Cancer treatment can lead to severe fungal infections (candidiasis, called thrush) in the mouth. This can cause pain, difficulties in eating and longer hospital stays. Infection can sometimes spread through the body and become life-threatening. Different drugs are used to try and relieve candidiasis. There is insufficient evidence that any of the antifungal drugs may cure fungal infections in the mouth for people with cancer and more research is needed.

BACKGROUND

Treatment of solid malignant tumours and the leukemias 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 oral mucosa. 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).

Patients with cancer are advised to maintain oral hygiene. Depending on the cancer centre, the patient's age and the expected toxicity of their treatment protocol, additional agents may be provided to prevent oral complications. Nevertheless, oral complications remain a major source of illness despite the use of a variety of agents to prevent them. A recent Cochrane review looked at the use of oral and topical prophylactic agents for the prevention of oral candidiasis in patients with cancer treated by chemotherapy (Clarkson 2007a). The review concluded that there is strong evidence, from randomised controlled trials, that drugs absorbed or partially absorbed from the gastrointestinal (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. This present review follows on from this and looks at the treatment of overt oral candidiasis in patients receiving treatment for cancer. This review is one in a series of four Cochrane reviews looking at the prevention and treatment of both oral candidiasis and oral mucositis (Clarkson 2007a; Clarkson 2007b; Worthington 2007).

OBJECTIVES

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

The following primary null hypothesis was tested for comparisons between groups treated for oral candidiasis:
There is no difference in the proportion of patients without oral candidiasis after treatment.

The primary outcomes were therefore:

- Eradication of candidiasis
- Improvement of candidiasis.

In this review we proposed to address the hypothesis of no difference between groups treated for oral candidiasis for the following secondary outcomes if data were available from studies which included a primary outcome:

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

The following subgroup analyses were proposed:

- Cancer type (leukaemia, solid cancer and mixed)
- Cancer treatment type
- Age group (children, adults, children and adults).

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials were eligible for inclusion in this review.

Types of participants

Anyone with cancer who received chemotherapy or radiotherapy or both and had overt oral candidiasis.

Types of interventions

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

Types of outcome measures

Primary outcome:

- Oral candidiasis (absent or present)

Secondary outcomes:

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

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 searches:

The following databases were searched:
Cochrane Oral Health Group Trials Register (whole database, to 1 June 2010) (see Appendix 1)
Cochrane Pain, Palliative and Supportive Care (PaPaS) Group Trials Register (whole database, to 1 June 2010) (see Appendix 1)
Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 2; searches conducted 1 June 2010) (see Appendix 2)

MEDLINE via OVID (1950 to 1 June 2010) (see Appendix 3)
EMBASE via OVID (1980 to 1 June 2010) (see Appendix 4)
CINAHL via EBSCO (1980 to 1 June 2010) (see Appendix 5)
CANCERLIT via PubMed (1950 to 1 June 2010) (see Appendix 6)
OpenSIGLE (1980 to 1 June 2010) (see Appendix 7)
LILACS via the Virtual Health Library (1980 to 1 June 2010) (see Appendix 8)

Sensitive search strategies were developed for each database using a combination of free text and MeSH terms. The MEDLINE and CANCERLIT subject searches were conducted with the addition of the *Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2009 revision)* as referenced in Chapter 6.4.11.1 and detailed in boxes 6.4.a and 6.4c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 (Higgins 2009). Filters developed by the Cochrane Oral Health Group for identifying randomised controlled trials were used for the searches of EMBASE and CINAHL. The LILACS subject search was linked to the Brazilian Cochrane Center search strategy for identifying randomised controlled trials in LILACs.

Searching other resources:

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 and LILACS. OpenSIGLE is no longer being updated and will not be searched for future updates of this review.

Data collection and analysis

Selection of studies

The titles and abstracts (when available) of all reports identified through the searches were scanned 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.

Data extraction and management

Data were extracted by two review authors independently using specially designed data extraction forms. The characteristics of the trial participants, interventions and outcomes for the included trials are presented in the study tables. Candidiasis was recorded as absent or present, and data for both clinical and mycological assessments were extracted. 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 conducted and whether a dentist was involved in the investigation. Trial authors were contacted for clarification or for further information.

Assessment of risk of bias in included studies

The assessment of risk of bias for included trials was undertaken independently and in duplicate by two review authors. Studies were analysed for the following to assess validity as a threshold for inclusion of the studies, which is described as one of the options in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 (Higgins 2009) on the following individual quality criteria:

- Adequate sequence generation: Yes, No, Unclear
- Allocation concealment: Yes, No, Unclear
- Blinding of participants and carers: Yes, No, Unclear
- Blinidng of outcome assessors: Yes, No, Unclear
- Incomplete outcome data addressed: Yes, No, Unclear
- Free of selective outcome reporting: Yes, No, Unclear
- Free of other biases: Yes, No, Unclear

'Yes' indicates a low risk of bias, 'No' indicates high risk of bias and 'Unclear' indicates either lack of information or uncertainty over the potential for bias. A risk of bias table was completed for each included study. Results are presented graphically by study (see Figure 1) and by domain over all studies (Figure 2) .

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

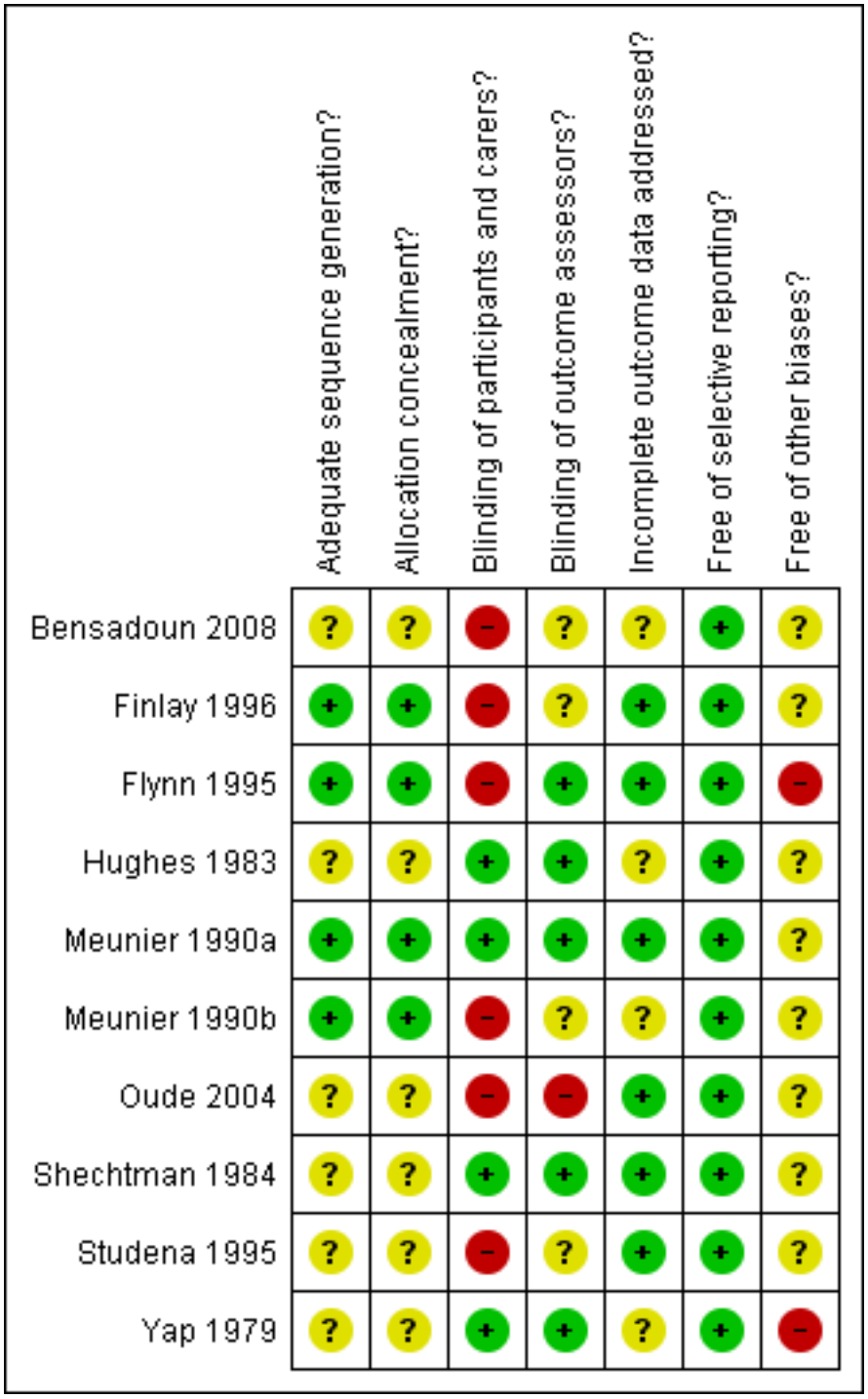
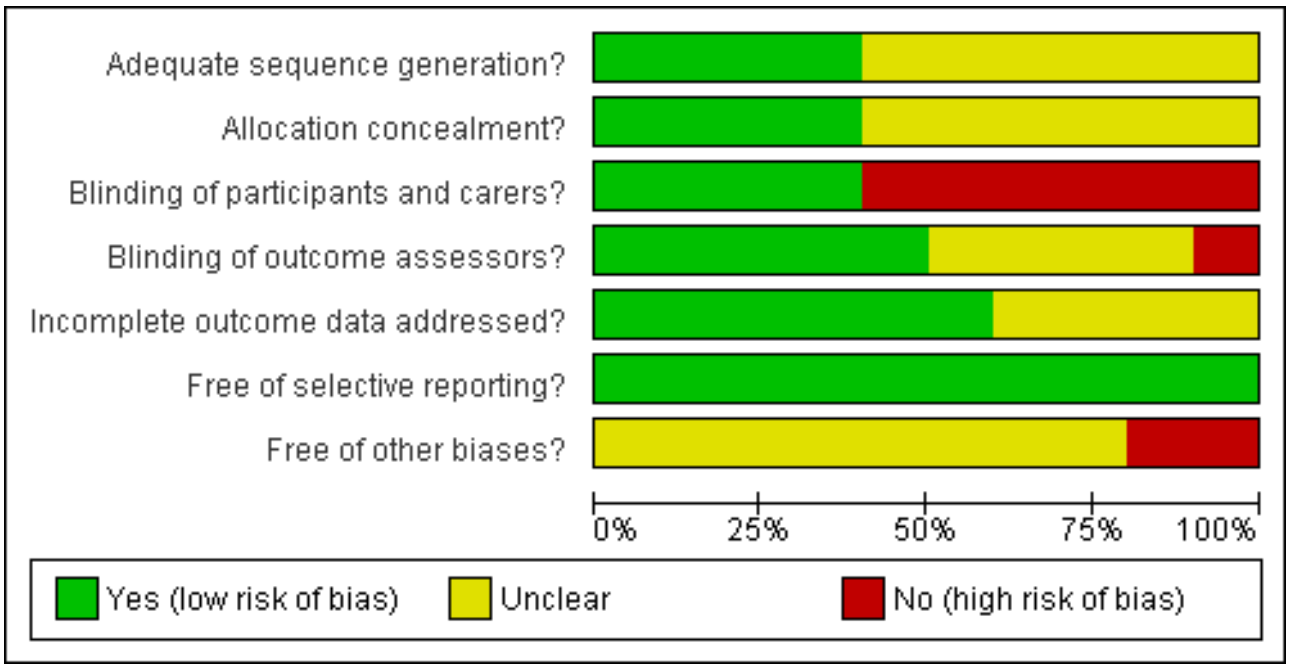


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Risk of bias was assessed for each study. Studies were considered to be at low risk of bias if there was adequate concealment of allocation, blinded outcome assessment and information on the reason for withdrawal provided by trial group. If one of these criteria was not met a study would be considered at moderate risk of bias, otherwise at high risk of bias.

Measure of treatment effect

For dichotomous outcomes, the estimates of effect of an intervention were expressed as risk ratios together with 95% confidence intervals. For continuous outcomes mean differences together with 95% confidence intervals were used.

Dealing with missing data

Intention-to-treat analysis was to be conducted where possible. Methods outlined in the handbook (Higgins 2009) were used to impute missing standard deviations if these could not be obtained from trial authors.

Assessment of heterogeneity

We planned to investigate clinical heterogeneity by examining the different cancer types and age groups, however there were insufficient trials looking at the same intervention to undertake this.

Assessment of reporting biases

We tabulated all the outcomes considered here.

Data synthesis

Meta-analyses were done only with studies of similar comparisons. Risk ratios were combined for dichotomous data using random-effects models (fixed-effect models used if less than 3 studies in meta-analysis).

Subgroup analysis and investigation of heterogeneity

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

We proposed a priori to conduct subgroup analyses for different cancer types (solid, leukaemia and mixed), different types of cancer treatment (chemotherapy, radiotherapy) and age groups (children, adults and mixed). There were insufficient trials by intervention type to undertake this.

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 quantified by I^2 statistics.

RESULTS

Description of studies

Results of the search

The search was conducted for the four similar reviews in this series (Clarkson 2007a; Clarkson 2007b; Worthington 2007) and has now been repeated seven times since 1999 for different updates. The most recent searches in October 2008, August 2009, January 2010 and June 2010 identified 1924, 621, 394 and 294 records respectively. Following screening of all three databases 125 potential trials were identified for the four reviews. There was only one further trial to be included in this review update (Bensadoun 2008) and one further study to be excluded (Yamaguchi 2006).

Included studies

See Characteristics of included studies table for further details. One included study included episodes (n = 60) rather than patients (n =

56), but as these numbers were similar we decided to include the study.

Setting

Of the 10 included trials, four were conducted in USA (Flynn 1995; Hughes 1983; Shechtman 1984; Yap 1979) and six in Europe (Bensadoun 2008; Finlay 1996; Meunier 1990a; Meunier 1990b; Oude 2004; Studena 1995). Six of the trials received external funding, three obtained government funding and five acknowledged assistance from the pharmaceutical industry. The providers and assessors of the treatments were mainly medical staff although one of the trials involved a dentist (Finlay 1996). None of the trials involved the patients in the outcome measurement.

Participants

The results of the 10 trials included in the review are based on 940 patients. The range of patients was from 6 to 141 per treatment or control group.

Six of the 10 trials recruited only adult patients with cancer, one included both adults and children (Hughes 1983), one included only children (Flynn 1995) and in two trials the age of the patients was unclear (Meunier 1990b; Shechtman 1984). The type of cancer being treated was a combination of leukemias and solid tumours in seven trials (Flynn 1995; Hughes 1983; Meunier 1990a; Meunier 1990b; Oude 2004; Shechtman 1984; Studena 1995), head and neck cancer in two trials (Bensadoun 2008; Finlay 1996), and children with unspecified malignancies in the remaining trial (Flynn 1995). Little information was provided on the cancer treatment regimens received by patients in the trials. In one trial only radiotherapy was used (Finlay 1996), one trial used both cytotoxic chemotherapy and radiotherapy (Oude 2004) and for one trial information was provided for individual patients regarding the use of steroids and antibiotics in addition to chemotherapy (Shechtman 1984). The diagnosis of oral candidiasis at entry into the trial was usually a combination of both clinical and mycological diagnosis. However in two trials only clinical diagnosis was used (Finlay 1996; Studena 1995).

Interventions

All of the 10 trials provided a clear description of the interventions including the dose and method of administration for both the test and control groups. In only two trials was a comparison made with a placebo (Hughes 1983; Shechtman 1984). The majority of trials (six) compared different test agents with varying doses, frequency and duration of use. Two trials compared different doses of a test agent used at the same frequency and duration (Bensadoun 2008; Yap 1979).

The interventions for the 10 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 (Finlay 1996; Flynn 1995; Meunier 1990a; Oude 2004; Studena 1995)
- ketoconazole (Hughes 1983; Meunier 1990a; Meunier 1990b)
- itraconazole (Oude 2004; Studena 1995).

Partially absorbed from the GI tract:

- clotrimazole (Shechtman 1984; Yap 1979).
- miconazole (Bensadoun 2008)

Not absorbed from the GI tract:

- amphotericin B (Finlay 1996)
- nystatin (Flynn 1995; Meunier 1990b).

Outcomes

There was variation between the trials in the assessment of oral candidiasis. All trials reported both a clinical and microbiological outcome of oral candidiasis. All trials used the dichotomous clinical outcome 'eradicated' verus 'not eradicated'. In addition two trials (Finlay 1996; Flynn 1995) compared the severity before and after treatment using a 4-point scoring system. For three trials (Meunier 1990b; Studena 1995; Yap 1979) the method of assessment was not given. Mycological assessments were based on cultures rather than smears in all trials and the dichotomous classification of eradicated or not could be obtained from all the 10 trials. Only in three trials were outcome measures of pain or dysphagia collected (Bensadoun 2008; Flynn 1995; Shechtman 1984) and only three reported side effects (Bensadoun 2008; Flynn 1995; Oude 2004).

Excluded Studies

See Characteristics of excluded studies table for further details.

Seventeen of the apparently eligible studies were excluded: four were not randomised controlled trials (Holst 1984; Jorgensen 2006; Urabe 1990; Walsh 2002); nine did not have just oral candidiasis for entry into the study (Anaissie 1996; Benhamou 1991; Bourhis 2004; Fleming 2001; Lake 1996; Lefebvre 2002; Subira 2004; Verweij 1994; Walsh 2004); in one study the data were presented in terms of episodes not patients (Kostiala 1982); two trials were excluded as the data were not presented in an accessible form (Conrad 1990; Domenge 1999); and one study conducted in Japan included patients who were not receiving treatment for cancer (Yamaguchi 2006).

Risk of bias in included studies

The kappa score between the two raters was one for each item assessed. Letters were sent to authors of the trials and only one replied (Finlay 1996), the information supplied changed the concealment of randomisation from unclear to adequate, and clarified the withdrawals.

One study was assessed as at low risk of bias (Meunier 1990a).The risk of bias assessment is summarised overall and for each trial in Figure 1 and Figure 2.

Adequate sequence generation

Adequate sequence generation was observed in four trials (40%), where a clear statement of the method of randomisation was reported. In the remainder of trials a judgment of 'unclear' was given as reporting lacked description with such statements as 'were randomised' or 'were stratified' appearing most commonly.

Allocation

Adequate allocation concealment was observed in the same four trials as above (40%). The remainder failed to indicate whether the generated randomisation sequence was concealed

from individuals involved in the enrolment and assignment of participants.

Blinding

In four trials (40%) participants and carers were blinded to the allocated intervention. This was not done for the remaining six trials. Blinding of outcome assessors was adequate for five trials (50%), four being unclear and one not blinded.

Incomplete outcome data

In six trials (60%), incomplete outcome data was assessed as adequate. In the remaining four trials it was unclear which group the patients who were excluded for specific reasons belonged to.

Selective reporting

We consider all trials to be free of selective reporting as the primary outcomes were included in all.

Other potential sources of bias

This was unclear in eight trials and assessed as 'no' in two (Flynn 1995; Yap 1979) due to there being a unit of analysis problem with episodes rather than patients being used for the analysis. As the number of episodes was similar to the number of patients in both (60 and 56 in Flynn 1995; 186 and 180 in Yap 1979), episodes were used in the data analysis.

Effects of interventions

Comparison 1, Outcome 1.1 - Clinical: eradication of oral candidiasis

One of the two placebo controlled trials found a significant benefit (risk ratio (RR) = 3.61, 95% confidence interval (CI) 1.47 to 8.88) for patients taking the absorbed drug ketoconazole (Hughes 1983). In the other placebo controlled trial on the partially absorbed drug, clotrimazole, no benefit was demonstrated (Shechtman 1984).

Three trials compared different types of absorbed drugs with each other and they failed to demonstrate a benefit of one drug against another: one trial compared fluconazole with ketoconazole (Meunier 1990a); two trials fluconazole versus itraconazole (Oude 2004; Studena 1995).

Three trials compared absorbed drugs (ketoconazole or fluconazole) with drugs not absorbed (nystatin or amphotericin B). Two of these trials demonstrated a significant clinical benefit of the absorbed drug fluconazole over the non-absorbed drug nystatin (Finlay 1996; Flynn 1995), and the meta analysis found a benefit for the absorbed drugs over the non-absorbed drugs (RR = 1.29, 95% CI fixed 1.09 to 1.52; Chi^2 for heterogeneity P = 0.01). However there was substantial heterogeneity between the three trials with I^2 = 78%.

One trial compared different doses of a partially absorbed drug, clotrimazole, and failed to find a significant difference (Yap 1979) (RR = 1.00, 95% CI 0.90 to 1.11).

A further trial compared the partially absorbed drug miconazole at different doses as a tablet and gel and found no statistically significant difference in eradication of candidiasis (Bensadoun 2008).

Comparison 1, Outcome 1.2 - Mycological: eradication of oral candidiasis

There were some differences between the results for the mycological assessments compared with those from the clinical assessment. Despite a significant clinical improvement there was no statistically significant difference in mycological eradication between an absorbed drug ketoconazole and placebo (Hughes 1983). However, there was evidence of different eradication rates with different absorbed drugs and a statistically significant benefit was found for fluconazole over itraconazole (RR = 1.17, 95% CI 1.04 to 1.33; Chi^2 for heterogeneity P = 0.30). In agreement with the clinical assessment there was a statistically significant difference in terms of a benefit for absorbed drugs compared to not absorbed drugs (RR = 1.82, 95% CI 1.28 to 2.57; Chi^2 for heterogeneity P = 0.001). One further trial (Yap 1979) demonstrated that 50 mg of the partially absorbed drug clotrimazole eradicated more cases than the lower dose of 10 mg (RR = 2.00, 95% CI 1.11 to 3.60).

None of the studies reported: relief of pain, relief of dysphagia, incidence of systemic infection, amount of analgesia, days stay in hospital, cost of oral care, patient quality of life.

DISCUSSION

Whilst we have been able to achieve our objective in evaluating the effectiveness of interventions to treat oral candidiasis, there were insufficient trials to make strong recommendations for patient care. The generalisability of the results is difficult to comment on as reporting of the types of cancer and details of treatment was unclear and few trials included children.

There were only two trials that compared the treatment of candidiasis using an active drug with a placebo. There was some evidence, based on one trial, that ketoconazole is effective, but there is a need for more trials that include a placebo group. The risk of hepatotoxicity with prolonged use of ketoconazole could influence treatment decisions and the UK Committee on Safety of Medicines has recommended that prescibers should weigh up the potential benefits against the risk of liver damage, and should carefully monitor patients both clinically and biochemically (BNF 2009).

There is evidence that absorbed drugs are more effective than drugs not absorbed from the gastrointestinal tract. There was no difference found in either trial comparing two absorbed drugs, and there was an indication that a higher dose of clotrimazole was more effective than a lower dose, although this was only found for the mycological assessment. There were no trials comparing partially absorbed drugs with either absorbed drugs or drugs not absorbed.

The findings from this review are disappointing as there were only 10 trials including 940 patients, 69 of whom were included in the two trials with placebo control groups. This is far fewer than the 28 trials with 4226 patients included in the prevention review (Clarkson 2007a).

There was limited consistency between trials on the clinical diagnosis of oral candidiasis and there was also little reported in terms of relief of pain, relief of dysphagia, incidence of systemic infection, amount of analgesia, days stay in hospital, cost of oral care 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 the justification for conducting trials.

It is not possible to assess whether there was any evidence of publication bias however, with few trials and patients, this could be a major problem.

For patients being treated for cancer the clinical dilemma is whether to prevent or treat oral candidiasis. The findings from the prevention review would suggest that if the incidence of oral candidiasis for a patient subgroup is likely to be high then a drug absorbed or partially absorbed from the gastrointestinal tract should be prescribed at the start of cancer treatment. The incidence of oral candidiasis is variable and depends on the nature of the underlying disease and the intensity of treatment. For absorbed drugs in populations with an incidence of 20% (mid range of results in control groups), the number needed to treat (NNT) to prevent one extra case of oral candidiasis was 9 (95% confidence interval 7 to 13) (Clarkson 2007a).

The findings of this review should be considered in the context of the general medical management of patients with cancer. A review investigating the routine use of antifungal therapy in cancer patients did not find an effect on mortality and only a modest effect on systemic fungal invasion (Gotzsche 2002). The authors questioned the current widespread practice of prophylactic antifungal therapy and this finding should be considered when interpreting the results of this review where we are specifically looking at oral outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Clinicians need to make a decision on whether to prevent or treat oral candidiasis in patients receiving treatment for cancer. The evidence on which drug should be prescribed is weak and unreliable.

Implications for research

There is a need for more well designed trials that compare the effectiveness of drugs absorbed, partially absorbed or not absorbed from the gastrointestinal tract with a placebo control. These should be conducted before comparing specific agents with each other. The limited evidence of effectiveness of current therapies, combined with side-effects profiles of those agents with proven efficacy suggest that new interventions for treating oral candidiasis are needed.

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Anaissie EJ, Darouiche RO, Abi-Said D, Uzun O, Mera J, Gentry LO, et al. Management of invasive candidal infections: results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of the literature. *Clinical Infectious Diseases* 1996;**23**(5):964-72.

Benhamou 1991 *{published data only}*

Benhamou E, Hartmann O, Nogues C, Maraninchi D, Valteau D, Lemerle J. Does ketoconazole prevent fungal infection in children treated with high dose chemotherapy and bone marrow transplantation? Results of a randomized placebo-controlled trial. *Bone Marrow Transplantation* 1991;**7**(2):127-31.

Bourhis 2004 *{published data only}*

Bourhis JH. Caspofungin in the empirical treatment of fungal infections. *Journal de Mycologie Medicale* 2004;**14**(4 II):240-3.

Conrad 1990 *{published data only}*

Conrad DA, Lentnek AL. Comparitive evaluation on nystatin pastille and clotrimazole troche for the treatment of candidal stomatitis in immunocompromised patients. *Current Therapeutic Research, Clinical & Experimental* 1990;**47**(4):627-36.

Domenge 1999 *{published data only}*

Domenge C, Wibauld P, Tancrede C, Sube B, Leridant AM, Marandas P, et al. Randomized study of Fluconozole (FCA) oral solution (OS) versus amphotericin B (AB) oral solution in oropharingeal candidiasis (OPC) in head and neck cancer patients (HNCP) after radiotherapy. *Supportive Care in Cancer* 1999;**7**(Suppl. Abstr. P-180):210.

Fleming 2001 *{published data only}*

Fleming RV, Kantarjian HM, Husni R, Rolston K, Lim J, Raad I, et al. Comparison of amphotericin B lipid complex (ABLC) vs. ambisome in the treatment of suspected or documented fungal infections in patients with leukemia. *Leukemia and Lymphoma* 2001;**40**(5-6):511-20.

Holst 1984 *{published data only}*

Holst E. Natamycin and nystatin for treatment of oral candidiasis during and after radiotherapy. *The Journal of Prosthetic Dentistry* 1984;**51**(2):226-31.

Jorgensen 2006 *{published data only}*

Jorgensen KJ, Johansen HK, Gotzsche PC. Flaws in design, analysis and interpretation of Pfizer's antifungal trials of

voriconazole and uncritical subsequent quotations. *Trials* 2006;**7**:3.

Kostiala 1982 *{published data only}*

Kostiala I, Kostiala AAI, Elonen E, Valtonen VV, Vuopio P. Comparison of clotrimazole and chlorhexidine in the topical treatment of acute fungal stomatitis in patients with hematological malignancies. *Current Therapeutic Research* 1982;**31**(5):752-63.

Lake 1996 *{published data only}*

Lake DE, Kunzweiler J, Beer M, Buell DN, Islam MZ. Fluconazole versus amphotericin B in the treatment of esophageal candidiasis in cancer patients. *Chemotherapy* 1996;**42**(4):308-14.

Lefebvre 2002 *{published data only}*

Lefebvre JL, Domenge C. A comparative study of the efficacy and safety of fluconazole oral suspension and amphotericin B oral suspension in cancer patients with mucositis. *Oral Oncology* 2002;**38**(4):337-42.

Subira 2004 *{published data only}*

Subira M, Martino R, Gomez L, Marti JM, Estany C, Sierra J. Low-dose amphotericin b lipid complex vs. conventional amphotericin B for empirical antifungal therapy of neutropenic fever in patients with hematologic malignancies - a randomized, controlled trial. *European Journal of Haematology* 2004;**72**(5):342-7.

Urabe 1990 *{published data only}*

Urabe A, Takaku F, Mizoguchi H, Nomura T, Ogawa T, Maekawa T, et al. Prophylactic and therapeutic effects of oral administration of amphotericin B in mycosis associated with hematological diseases. *The Japanese Journal of Antibiotics* 1990;**43**(1):116-30.

Verweij 1994 *{published data only}*

Verweij PE, Donnelly JP, Kullberg BJ, Meis JF, De Pauw BE. Amphotericin B versus amphotericin B plus 5-flucytosine: poor results in the treatment of proven systemic mycoses in neutropenic patients. *Infection* 1994;**22**(2):81-5.

Walsh 2002 *{published data only}*

Walsh TJ, Lutsar I, Driscoll T, Dupont B, Roden M, Ghahramani P, et al. Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. *Pediatric Infectious Disease Journal* 2002;**21**(3):240-8.

Walsh 2004 *{published data only}*

Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *New England Journal of Medicine* 2004;**351**(14):1391-402.

CHARACTERISTICS OF STUDIES

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

Yamaguchi 2006 *{published data only}*

Yamaguchi H, Enomoto S, Kaku M, Sakamaki H, Tanaka K, Yoshida M. [An open randomized parallel-comparison study of itraconazole oral solution versus itraconazole capsules in treatment of patients with oropharyngeal candidiasis]. Japanese Journal of Chemotherapy 2006; Vol. 54, issue Suppl 1:18-31.

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BNF 2009

Joint Formulary Committee. British National Formulary. 57. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2009.

Clarkson 2007a

Clarkson JE, Worthington HV, Eden OB. Interventions for preventing oral candidiasis for patients with cancer receiving treatment. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [Art. No.: CD003807. DOI: 10.1002/14651858.CD003807.pub3]

Clarkson 2007b

Clarkson JE, Worthington HV, Eden OB. Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [Art. No.: CD001973. DOI: 10.1002/14651858.CD001973.pub3]

Gotzsche 2002

Gøtzsche PC, Johansen HK. Routine versus selective antifungal administration for control of fungal infections in patients with cancer. *Cochrane Database of Systematic Reviews* 2002, Issue 2. [Art. No.: CD000026. DOI: 10.1002/14651858.CD000026]

Higgins 2009

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 (updated September 2009). The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org.

Worthington 2007

Worthington HV, Clarkson JE, Eden OB. Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [Art. No.: CD000978. DOI: 10.1002/14651858.CD000978.pub3]

References to other published versions of this review

Clarkson 2004

Clarkson JE, Worthington HV, Eden OB. Interventions for treating oral candidiasis for patients with cancer receiving treatment. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [Art. No.: CD001972. DOI: 10.1002/14651858.CD001972.pub2]

Bensadoun 2008

Methods	Randomised, parallel group multicentre single blind study conducted in France, Tunsia and Morocco. Patients and carers not blinded. Primary outcome assessment made by blinded assessor. No evidence of funding apart from one collaborator is a consultant for pharmaceutical company who produced the tablets. Patients were recruited from May 2002 until June 2004.
Participants	Adults with head and neck cancer. 306 patients randomised, 154 to miconazole tablet and 152 to miconazole gel. 6 patients in each group had no treatment, analysis conducted on 141 patient in each group. OP confirmed by direct mycological examination (culture).
Interventions	2 groups: miconazole tablet Lauriad 50 mg MBT (kept in mouth as long as possible) or 500 mg miconazole gel MOG (applied to gums) once daily for 14 days.
Outcomes	Primary outcome success at day 14 (clinical eradication) and partial response was defined as improvement by 2 points on Murray Scoring Scale compared with score at baseline. Assessment made at 2, 6, 20 days, unclear which presented. Secondary endpoint was success at day 7. Improvement in clinical symptoms, mycological cure (culture), recurrence rate and safety also reported.
Notes	Modified intention-to-treat analysis - all randomised patients who received at least 1 treatment dose and had efficacy evaluation after randomisation. Non-inferiority statistical approach used. Authors contacted about assessor blinding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "patients were randomised".
Allocation concealment?	Unclear risk	Not reported.
Blinding of participants and carers?	High risk	Comment: Tablet versus gel.
Blinding of outcome assessors?	Unclear risk	Quote: "An amendment introduced a blind assessment of the primary criterion performed in each investigational centre by an independent healthcare member who was unaware of the study drug allocated to each patient. It was implemented after the inclusion of 59 patients". Comment: lack of clarity about how this affected the results.
Incomplete outcome data addressed?	Unclear risk	Comment: Figure 1 provides clear description of patients for data analysis. Two patients were given the wrong intervention, 6 in each group did not receive treatment and 6 did not have an outcome assessment. Numbers do not add up and true intention to treat analysis was not undertaken.
Free of selective reporting?	Low risk	Comment: Both clinical and mycological assessment reported and other secondary outcomes.
Free of other biases?	Unclear risk	One author is consultant for pharmaceutical company who produced tablets for study.

Finlay 1996

Methods	Randomised, parallel group study conducted in Scotland. The patients were not blinded. Information on withdrawals clarified by letter. No mention of funding but possible university funding. No dates for recruitment period.
Participants	Adults with head and neck cancer. 77 enrolled, 73 completed.
Interventions	2 groups. Fluconazole 50 mg daily for 7 days. Amphotericin B 10 mg lozenge sucked for 14 days.
Outcomes	Clinical and mycological eradication (culture). Assessment made at 2, 6, 20 days, unclear which presented.
Notes	Communicating with authors changed randomisation assessment from Unclear to Yes (low risk of bias).

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Comment: Changed after clarification by authors.
Allocation concealment?	Low risk	Comment: Changed after clarification by authors.
Blinding of participants and carers?	High risk	Comment: Tablet (7 days) versus lozenge (14 days).
Blinding of outcome assessors?	Unclear risk	Comment: Unclear for clinical assessment and mycological assessment.
Incomplete outcome data addressed?	Low risk	Comment: Clarified by authors.
Free of selective reporting?	Low risk	Comment: Clinical and mycological eradication.
Free of other biases?	Unclear risk	No information on funding.

Flynn 1995

Methods	Randomised, multicentre, parallel group study conducted in USA. Patient, carer not blind, assessor blind. Clear information on withdrawals given. Pfizer provided the drugs but no funding mentioned. No dates for recruitment period.
Participants	Children with malignancies and immunocompromised including HIV (data presented separately). 186 enrolled, 182 received drugs, 92 (cancer patients) completed.
Interventions	2 groups. Fluconazole 4 mg/kg suspension day 1 then 2 mg/day. Nystatin 4 ml USP suspension 4 times daily- swished in mouth and swallowed. Both for 14 days in total.
Outcomes	Clinical and mycological eradication (culture). Assessment at 7 days or later.
Notes	Study also included children with HIV, but data were presented separately. The dose of fluconazole was changed 1/4 way into study to 2 mg/kg day 1, then 3 mg/kg.

Risk of bias

Flynn 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "....patients were randomly assigned to receive....A computer generated random number code was supplied to each centre by Pfizer Central Research".
Allocation concealment?	Low risk	Quote: "The randomisation code was held by the pharmacist; neither patient nor physician had knowledge of the category of assignment before enrolment".
Blinding of participants and carers?	High risk	Comment: Drugs given at different frequencies.
Blinding of outcome assessors?	Low risk	Quote: "All clinical assessments were performed by investigators unaware of the subjects treatment regime".
Incomplete outcome data addressed?	Low risk	Comment: Clear explanation of withdrawals by intervention but not for cancer patients as separate group.
Free of selective reporting?	Low risk	Comment: Clinical and mycological eradication (culture).
Free of other biases?	High risk	6 patients were re-enrolled and treated as new patients - lack of independence of data. No reference to funding although Pfizer provided drug.

Hughes 1983

Methods	Randomised, parallel group study conducted in USA. Patient, carer and assessor blind. Unclear information on withdrawals given. Pharmaceutical company provided the tablets but no other information about funding. No dates for recruitment period.
Participants	Children and adults with mixed cancer. 64 enrolled, 56 completed.
Interventions	2 groups, placebo versus ketoconazole. 200 mg twice/day. 2 weeks duration.
Outcomes	Clinical and mycological eradication (culture). Assessment made at day 14.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "Randomised in a double blind placebo controlled study".
Allocation concealment?	Unclear risk	Comment: Drug supplied by pharmaceutical company but concealment still unclear.
Blinding of participants and carers?	Low risk	Quote: "Randomised in a double blind placebo controlled study".
Blinding of outcome assessors?	Low risk	Quote: "Randomised in a double blind placebo controlled study".

Hughes 1983 *(Continued)*

Incomplete outcome data addressed?	Unclear risk	8 patients (12%) withdrawn 5 for noncompliance and 3 by request, but unclear which group.
Free of selective reporting?	Low risk	Comment: Clinical and mycological eradication (culture).
Free of other biases?	Unclear risk	No information on funding except being given drug by pharmaceutical company.

Meunier 1990a

Methods	Randomised, parallel group study conducted in Belgium. Patient, carer, assessor blind. No clear information on withdrawals given. No information on funding except all study drugs supplied by Pfizer. No dates for recruitment period.
Participants	Adults with mixed cancer. 40 patients enrolled, 37 completed.
Interventions	2 groups. Ketoconazole 2 x 200 mg, once/day. Fluconazole 2 x 250 mg/day. Duration of therapy from 4 to 27 days, median 14 days.
Outcomes	Clinical eradication, and improvement. Assessment made at days 4 to 27. Microbiological eradication of initial pathogen (culture).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "Randomisation chart".
Allocation concealment?	Low risk	Quote: "All study drugs were supplied by Pfizer and were administered in identical capsules".
Blinding of participants and carers?	Low risk	Quote: "All study drugs were supplied by Pfizer and were administered as identical capsules".
Blinding of outcome assessors?	Low risk	Quote: "....double-blind".
Incomplete outcome data addressed?	Low risk	Quote: "Forty patients enrolled in the study, 3 were excluded (8%) before the code was opened". Comment: The reasons were given but not by group as the code was not broken. It is felt not to be a source of bias.
Free of selective reporting?	Low risk	Comment: Clinical and mycological eradication (culture).
Free of other biases?	Unclear risk	No information on funding except all study drugs supplied by Pfizer.

Meunier 1990b

Methods	Randomised, parallel group study conducted in Belgium. Patient, carer not blind, unclear whether assessor blind. Unclear information on withdrawals. No information about funding. No dates for recruitment period.
Participants	Patients with mixed cancer. 42 patients evaluated.
Interventions	2 groups. Ketoconazole tablets 200 mg every 8 hours. Nystatin 1000000 U suspension every 8 hours. Mean duration of ketoconazole was 13 days, nystatin 10 days, with maximum of 23 days for both groups.
Outcomes	Clinical eradication of oropharyngeal candidiasis or oral thrush. Microbiological eradication of pathogen (culture).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "Patients were randomly allocated to one of the two arms of the study using a randomisation list".
Allocation concealment?	Low risk	Quote: "The allocations were placed in sealed envelopes numbered sequentially". Quote: "Randomisation was done by one of the investigators following the numerical order".
Blinding of participants and carers?	High risk	Comment: tablets and suspension.
Blinding of outcome assessors?	Unclear risk	No information.
Incomplete outcome data addressed?	Unclear risk	Comment: 2 ketoconazole patients had early discontinuation. All other patients were treated for at least 10 days. In nystatin group 3 patients died. It is unclear whether these patients were included in the 42 or not.
Free of selective reporting?	Low risk	Comment: Clinical and mycological eradication(culture) .
Free of other biases?	Unclear risk	No information about funding.

Oude 2004

Methods	Randomised, parallel group, multicentre study conducted in Europe. Patients, carer and assessor not blind, but mycological assessment. No withdrawals. No information on funding. Recruitment between January 1992 and October 1997.
Participants	Adults with mixed cancer. 279 randomised but only 252 eligible and evaluated. Of the 27 patients 23 were not eligible and 4 had no CRF.
Interventions	2 groups. Fluconazole capsules 100 mg per day for 10 days. Itraconazole capsules 200 mg per day for 15 days.

Oude 2004 *(Continued)*

Outcomes	Clinical and mycological eradication at day 15 (culture). Evaluated at days 3, 7, 10, 15 and post-treatment assessment at day 42.
Notes	It is surprising that the study was not published for 7 years.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "....patients were randomised....".
Allocation concealment?	Unclear risk	No information.
Blinding of participants and carers?	High risk	Quote: "An open multicentre comparative study....".
Blinding of outcome assessors?	High risk	Quote: "An open multicentre comparative study....".
Incomplete outcome data addressed?	Low risk	Comment: 4 patients had no CRF but unclear which group however we felt this was unlikely to cause bias.
Free of selective reporting?	Low risk	Comment: Clinical and mycological eradication (culture) .
Free of other biases?	Unclear risk	No information on funding.

Shechtman 1984

Methods	Randomised, parallel group study conducted in USA. Patient, carer and assessor blind. Clear explanation of withdrawals. Funding from pharmaceutical company and charity. No dates for recruitment period.
Participants	Adults with mixed cancer. 16 enrolled, 13 completed.
Interventions	2 groups, placebo versus clotrimazole 10 mg troche of clotrimazole 5 times/day (dissolving for 15 to 30 minutes). Duration 48 hours to 4 weeks.
Outcomes	Clinical improvement with intention-to-treat analysis. Mycological not eradicated (culture). Unclear when assessment made.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "Eight patients were assigned by random allocation....".
Allocation concealment?	Unclear risk	No information given.
Blinding of participants and carers?	Low risk	Quote "....double blind clinical trial ....".

Shechtman 1984 *(Continued)*

		Quote: "Neither the patient, microbiologist, physician or nurse know whether the patients were receiving placebo or clotrimazole".
Blinding of outcome assessors?	Low risk	Quote "....double blind clinical trial....". Quote: "Neither the patient, microbiologist, physician or nurse know whether the patients were receiving placebo or clotrimazole".
Incomplete outcome data addressed?	Low risk	Comment: 4 patients lost to follow-up (25%), 2 in each group with known reasons.
Free of selective reporting?	Low risk	Comment: Clinical and mycological eradication (culture).
Free of other biases?	Unclear risk	Industry funding and charity grant. Miles pharmaceuticals provided "coded" drugs.

Studena 1995

Methods	Randomised, parallel group study conducted in Slovac Republic. Patient, carer, not blind, unclear if assessor blind. Funding unclear. Recruitment 1.5.1992 until 1.5.1994.
Participants	Adults with mixed cancer. 53 randomised and completed.
Interventions	2 groups. Fluconazole 10 days 100 mg OD or itraconazole 100 mg BID 15 days.
Outcomes	Clinical and mycological eradication (culture) at 15 and 42 days.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "Patients were randomised....".
Allocation concealment?	Unclear risk	Comment: No information given.
Blinding of participants and carers?	High risk	Comment: Drugs taken over different periods.
Blinding of outcome assessors?	Unclear risk	Comment: No information given.
Incomplete outcome data addressed?	Low risk	Quote: "All cancer patients with neutrophil count more than 500 hospitalised at the National Cancer Centre clinical of the Post Graduate Medical School and Medical Faculty from 1.5.1992 to 1.5.1994 (53 patients) were randomised." Comment: Analysis on 53 patients, so no drop outs.
Free of selective reporting?	Low risk	Comment: Clinical and mycological eradication (culture).
Free of other biases?	Unclear risk	No information about funding.

Yap 1979

Methods	Randomised, parallel group study conducted in USA. Patient, carer, assessor blind. No clear explanation of withdrawals. Pharaceutical and government funding. No recruitment dates given.
Participants	Adults with mixed cancer. 56 patients, 60 episodes enrolled. 52 episodes, 48 patients completed.
Interventions	2 groups. 10 mg versus 50 mg troche clotrimazole, for 14 days.
Outcomes	Clinical and mycological eradication (culture). Unclear when assessment made.
Notes	As number of episodes 60 nearly same as number of patients so episodes used in analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "A randomised double blind trial....". Quote: "....a randomised double blind technique was used to divide the patients into two groups....".
Allocation concealment?	Unclear risk	No information given.
Blinding of participants and carers?	Low risk	Quote: "A randomised double blind trial....".
Blinding of outcome assessors?	Low risk	Quote: "A randomised double blind trial....".
Incomplete outcome data addressed?	Unclear risk	Quote: "56 cancer patients with 60 episodes of oropharyngeal candidiasis were entered into he study between September 1976 and September 1977". Quote: "Eight patients 8 episodes were considered inevaluable". Of the remaining 48 patients there were 52 episodes of infection. Comment: We don't know which group these patients were in.
Free of selective reporting?	Low risk	Comment: Clinical and mycological eradication (culture).
Free of other biases?	High risk	Quote: "If there was no clinical improvement after 5 days or the patients condition necessitated the start of systemic antifungal therapy, administration of the troches was discontinued". Possible bias due to episodes rather than patients and data not independent. Comment: Pharmaceutical and government funding.

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

Study	Reason for exclusion
Anaissie 1996	Patients with invasive candidiasis from 2 or more body sites were included (fluconazole versus amphotericin B).

Study	Reason for exclusion
Benhamou 1991	Patients with and without fungal infection were included in study (ketoconazole versus placebo).
Bourhis 2004	Empirical treatment of suspected fungal infections in neutropenic patients with fever.
Conrad 1990	AIDS and malignancy patients. Data not presented separately (nystatin versus clotrimazole).
Domenge 1999	Abstract, insufficient information (fluconazole versus amphotericin).
Fleming 2001	Patients had 5 different conditions for entry including invasive fungal infection (amphotericin B versus AmBisome).
Holst 1984	Not RCT (natamycin versus nystatin).
Jorgensen 2006	Note on Walsh 2004, which is excluded (caspofungin versus amphotericin).
Kostiala 1982	Episodes (85) not patients (53) (clotrimazole versus chlorhexidine).
Lake 1996	Esophageal candidiasis present for entry into the study (fluconazole versus amphotericin B).
Lefebvre 2002	Not all patients had oral candidiasis at the start of study (fluconazole versus amphotericin B).
Subira 2004	All patients had to be hospitalised for neutropenic fever, but did not necessarily have oral candidiasis at entry to study (amphotericin B).
Urabe 1990	Unclear if RCT (amphotericin B).
Verweij 1994	Patients had histologically proved systemic mycosis for entry into the study (amphotericin B versus amphotericin B plus 5-flucytosine).
Walsh 2002	Not RCT (voriconazole).
Walsh 2004	Empirical therapy only treating patients with infection (caspofungin versus amphotericin).
Yamaguchi 2006	Patients who did not have cancer were included (translated from Japanese).

RCT = randomised controlled trial

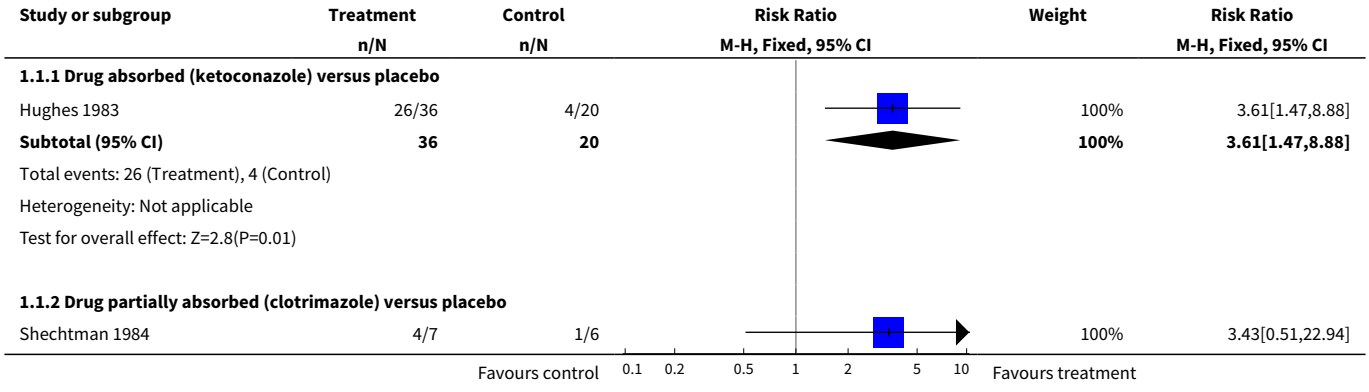
DATA AND ANALYSES

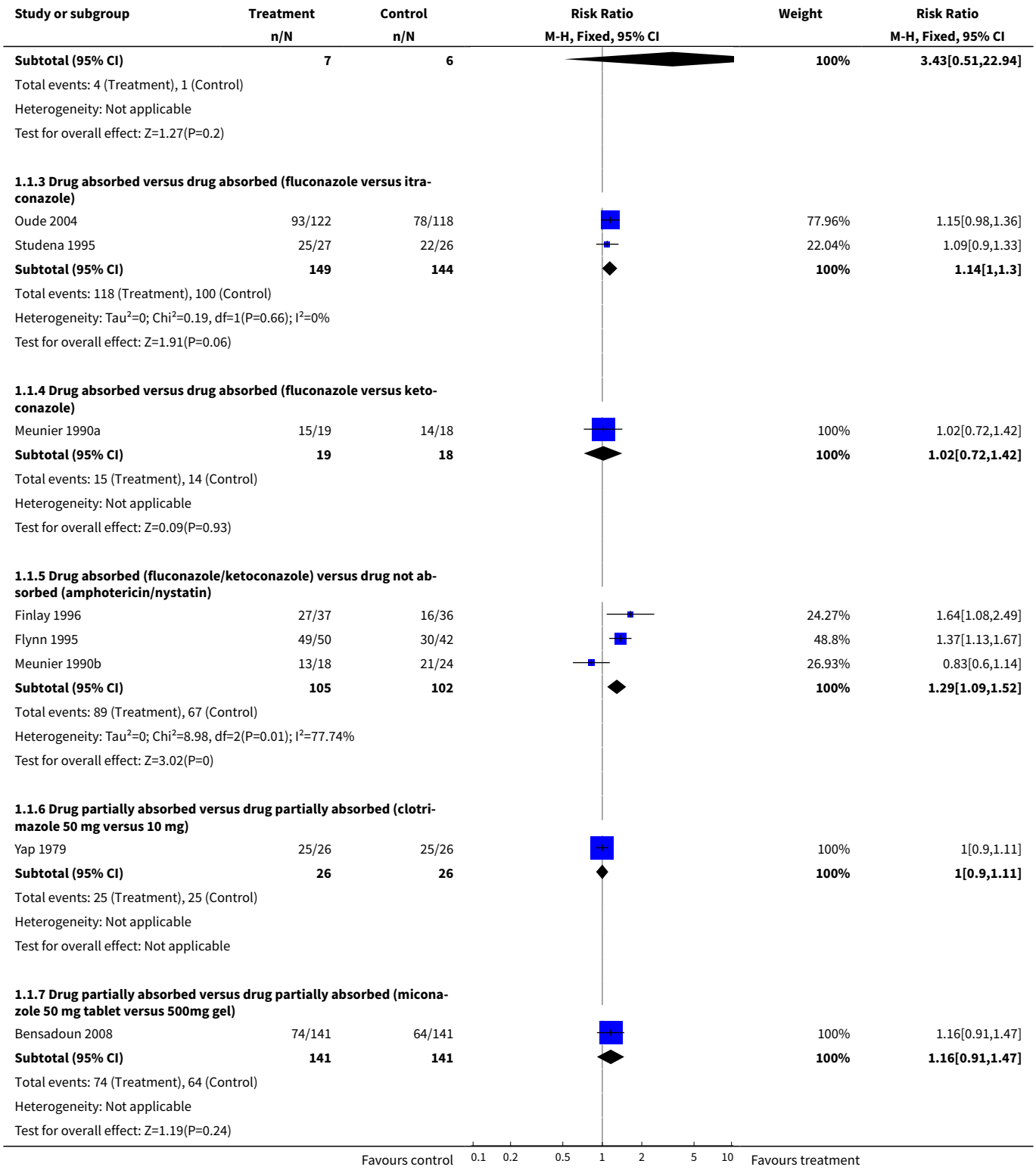
Comparison 1. All studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical: eradication of oral candidiasis	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Drug absorbed (ketoconazole) versus placebo	1	56	Risk Ratio (M-H, Fixed, 95% CI)	3.61 [1.47, 8.88]
1.2 Drug partially absorbed (clotrimazole) versus placebo	1	13	Risk Ratio (M-H, Fixed, 95% CI)	3.43 [0.51, 22.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Drug absorbed versus drug absorbed (fluconazole versus itraconazole)	2	293	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.00, 1.30]
1.4 Drug absorbed versus drug absorbed (fluconazole versus ketoconazole)	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.72, 1.42]
1.5 Drug absorbed (fluconazole/ketoconazole) versus drug not absorbed (amphotericin/nystatin)	3	207	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.09, 1.52]
1.6 Drug partially absorbed versus drug partially absorbed (clotrimazole 50 mg versus 10 mg)	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.90, 1.11]
1.7 Drug partially absorbed versus drug partially absorbed (miconazole 50 mg tablet versus 500mg gel)	1	282	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.91, 1.47]
2 Mycological: eradication of oral candidiasis	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Drug absorbed (ketoconazole) versus placebo	1	47	Risk Ratio (M-H, Fixed, 95% CI)	5.09 [0.73, 35.49]
2.2 Drug partially absorbed (clotrimazole) versus placebo	1	13	Risk Ratio (M-H, Fixed, 95% CI)	6.13 [0.38, 99.14]
2.3 Drug absorbed versus drug absorbed (fluconazole versus itraconazole)	2	291	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.04, 1.33]
2.4 Drug absorbed versus drug absorbed (fluconazole versus ketoconazole)	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.52, 1.72]
2.5 Drug absorbed (fluconazole/ketoconazole) versus not absorbed (amphotericin/nystatin)	3	189	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.28, 2.57]
2.6 Drug partially absorbed versus partially absorbed (clotrimazole 50 mg versus 10 mg)	1	52	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [1.11, 3.60]

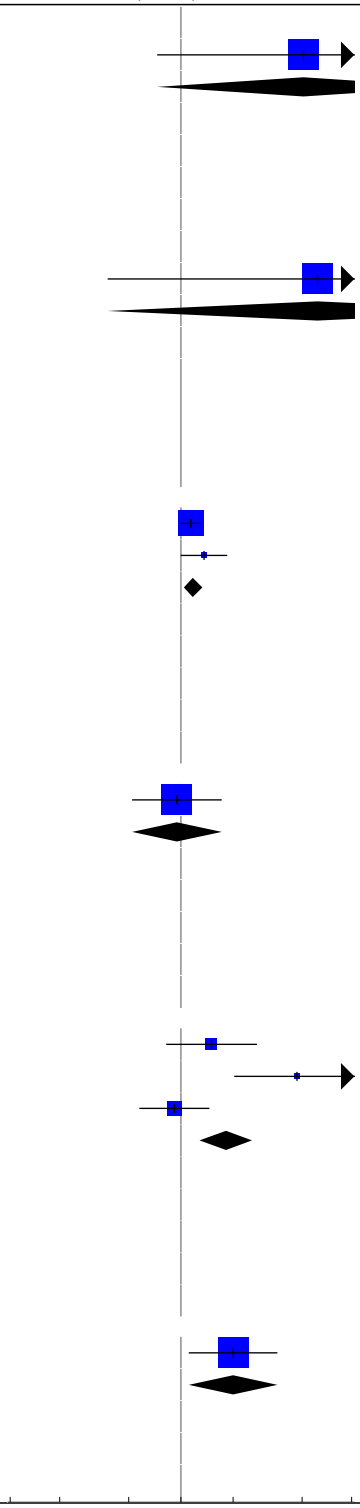
Analysis 1.1. Comparison 1 All studies, Outcome 1 Clinical: eradication of oral candidiasis.





Analysis 1.2. Comparison 1 All studies, Outcome 2 Mycological: eradication of oral candidiasis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Drug absorbed (ketoconazole) versus placebo					
Hughes 1983	12/33	1/14		100%	5.09[0.73,35.49]
Subtotal (95% CI)	**33**	**14**		**100%**	**5.09[0.73,35.49]**
Total events: 12 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.64(P=0.1)					
1.2.2 Drug partially absorbed (clotrimazole) versus placebo					
Shechtman 1984	3/7	0/6		100%	6.13[0.38,99.14]
Subtotal (95% CI)	**7**	**6**		**100%**	**6.13[0.38,99.14]**
Total events: 3 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.28(P=0.2)					
1.2.3 Drug absorbed versus drug absorbed (fluconazole versus itraconazole)					
Oude 2004	101/121	86/117		83.47%	1.14[0.99,1.3]
Studena 1995	24/27	17/26		16.53%	1.36[1,1.85]
Subtotal (95% CI)	**148**	**143**		**100%**	**1.17[1.04,1.33]**
Total events: 125 (Treatment), 103 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.09, df=1(P=0.3); I^2=8.51%					
Test for overall effect: Z=2.53(P=0.01)					
1.2.4 Drug absorbed versus drug absorbed (fluconazole versus ketoconazole)					
Meunier 1990a	10/19	10/18		100%	0.95[0.52,1.72]
Subtotal (95% CI)	**19**	**18**		**100%**	**0.95[0.52,1.72]**
Total events: 10 (Treatment), 10 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.18(P=0.86)					
1.2.5 Drug absorbed (fluconazole/ketoconazole) versus not absorbed (amphotericin/nystatin)					
Finlay 1996	17/37	11/36		36.67%	1.5[0.82,2.75]
Flynn 1995	29/41	5/33		18.22%	4.67[2.03,10.72]
Meunier 1990b	11/18	16/24		45.1%	0.92[0.58,1.46]
Subtotal (95% CI)	**96**	**93**		**100%**	**1.82[1.28,2.57]**
Total events: 57 (Treatment), 32 (Control)					
Heterogeneity: Tau^2=0; Chi^2=13.65, df=2(P=0); I^2=85.35%					
Test for overall effect: Z=3.35(P=0)					
1.2.6 Drug partially absorbed versus partially absorbed (clotrimazole 50 mg versus 10 mg)					
Yap 1979	18/26	9/26		100%	2[1.11,3.6]
Subtotal (95% CI)	**26**	**26**		**100%**	**2[1.11,3.6]**
Total events: 18 (Treatment), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.31(P=0.02)					



APPENDICES

Appendix 1. Cochrane Oral Health Group Trials Register; Cochrane Pain, Palliative & Supportive Care 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. The Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

Search strategy for the Cochrane Library

1. Exp NEOPLASMS
2. Exp LEUKEMIA
3. Exp LYMPHOMA
4. Exp RADIOTHERAPY
5. Exp BONE MARROW TRANSPLANTATION
6. neoplasm* or cancer* or carcino* or malignan*
7. leukemi* or leukaemia*
8. tumour* or tumor*
9. neutropeni*
10. adenocarcinoma*
11. lymphoma*
12. (radioth* or radiat* or irradiat* or radiochemo*)
13. (bone next marrow next transplant*)
14. chemo* or radiochemo*
15. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14)
16. Exp STOMATITIS
17. MUCOSITIS
18. CANDIDIASIS ORAL
19. stomatitis
20. (stevens next johnson next syndrome)
21. mucositis
22. oral near cand*
23. mouth near cand*
24. oral and fung*
25. mouth and fung*
26. (mycosis or mycotic or thrush)
27. #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
28. #15 AND #27

Appendix 3. MEDLINE via OVID search strategy

1. exp NEOPLASMS/
2. exp LEUKEMIA/
3. exp LYMPHOMA/
4. exp RADIOTHERAPY/
5. Bone Marrow Transplantation/
6. neoplasm$.mp.
7. cancer$.mp.
8. (leukaemi$ or leukemi$).mp.
9. (tumour$ or tumor$).mp.
10. malignan$.mp.
11. neutropeni$.mp.

12. carcino$.mp.
13. adenocarcinoma$.mp.
14. lymphoma$.mp.
15. (radioth$ or radiat$ or irradiat$).mp.
16. (bone adj marrow adj5 transplant$).mp.
17. chemo$.mp.
18. or/1-17
19. exp STOMATITIS/
20. Candidiasis, Oral/
21. stomatitis.mp.
22. mucositis.mp.
23. (oral and cand$).mp.
24. (oral adj6 mucos$).mp.
25. (oral and fung$).mp.
26. (mycosis or mycotic).mp.
27. or/19-26
28. 18 and 27

The above search was linked to the *Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2009 revision)* as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of *The Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.0.2 [updated September 2009].

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. exp animals/ not humans.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$).mp.
7. (radioth$ or radiat$ or irradiat$ or radiochemo$).mp.
8. (bone marrow adj3 transplant$).mp.
9. chemo$.mp.
10. or/1-9
11. exp Stomatitis/
12. Thrush/
13. (stomatitis or mucositis or (oral and candid$) or (oral adj4 mucositis) or (oral and fung$) or mycosis or mycotic or thrush).mp.
14. or/11-13
15. 10 and 14

The above search was linked to the Cochrane Oral Health Group filter for identifying randomized controlled trials in EMBASE:

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. CINAHLvia 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

The above search was linked to the Cochrane Oral Health Group search strategy for identifying randomized controlled trials in CINAHL:

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))

The above search strategy was linked to the *Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE via PubMed: sensitivity maximising version (2009 revision)* as referenced in Chapter 6.4.11.1 and detailed in box 6.4.a of *The Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.0.2 [updated September 2009].

(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. OpenSIGLE 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 via the Virtual Health Library search strategy

(www.bireme.org)

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$) OR (Tw oral AND Tw candidiasis$)

The above search was linked to the Brazilian Cochrane Center search strategy for identifying randomized controlled trials in LILACs:

((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)))

WHAT'S NEW

Date	Event	Description
9 June 2010	New search has been performed	Substantive amendment. Updated search found 1 new included trial and 1 excluded study. New methodology.
9 June 2010	New citation required but conclusions have not changed	New authorship.

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 1, 2002

Date	Event	Description
5 February 2007	New citation required but conclusions have not changed	Substantive amendment. An updated search in 2006 has found one more trial to include in this review, and seven more excluded studies. This update has updated references to other Cochrane reviews however the results and conclusions remain unchanged.

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. JC and HW independently and in duplicate assessed the eligibility of trials, extracted data and assessed the quality of the trials. HW conducted the statistical analysis which was interpreted by JC and HW. Tasneem Khalid provided advice on the interventions and Stefan Meyer and Martin McCabe provided input on the cancer treatments and the assessment of the candidiasis.

DECLARATIONS OF INTEREST

None known.

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INDEX TERMS

Medical Subject Headings (MeSH)

Antifungal Agents [pharmacokinetics] [*therapeutic use]; Candidiasis, Oral [*drug therapy] [metabolism]; Gastrointestinal Tract [metabolism]; Neoplasms [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans