Medical interventions for fungal keratitis (Review)

FlorCruz NV, Peczon IV, Evans JR

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[Intervention Review]

Medical interventions for fungal keratitis

Nilo Vincent FlorCruz[1], Ildefonso V Peczon[2], Jennifer R Evans[3]

[1]Department of Ophthalmology and Visual Sciences, University of the Phillipines-Philippine General Hospital, Manila, Philippines. [2]Department of Ophthalmology and Visual Sciences, Sentro Oftalmologico Jose Rizal, Manila, Philippines. [3]Cochrane Eyes and Vision Group, ICEH, London School of Hygiene & Tropical Medicine, London, UK

Contact address: Nilo Vincent FlorCruz, Department of Ophthalmology and Visual Sciences, University of the Phillipines-Philippine General Hospital, Taft Avenue, Manila, 1000, Philippines. docnilo11@gmail.com.

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ABSTRACT

Background

Fungal keratitis is a fungal infection of the cornea. It is common in agricultural tropical countries but relatively uncommon in developed countries. Although there are medications available, their effectiveness is unclear.

Objectives

To examine the effect of different antifungal drugs in the management of fungal keratitis.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2011, Issue 8), MEDLINE (January 1950 to August 2011), EMBASE (January 1980 to August 2011), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to August 2011), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 29 August 2011.

Selection criteria

We included all relevant randomised controlled trials (RCTs) on medical therapy for fungal keratitis.

Data collection and analysis

Two review authors selected studies for inclusion into the review, assessed trials for risk of bias and extracted data. Interventions were compared by the proportions of participants that did not heal after a specific time of therapy. No meta-analysis was performed because the trials studied different medications with different concentrations.

Main results

We included nine trials in this review; seven conducted in India, one in Bangladesh and one in Egypt. A total of 568 participants were randomised to the following comparisons: 1% topical itraconazole versus 1% topical itraconazole and oral itraconazole, different concentrations of silver sulphadiazine versus 1% miconazole, 1% silver sulphadiazine ointment versus 1% miconazole ointment, 2% econazole versus 5% natamycin, different concentrations of topical chlorhexidine gluconate versus 5% natamycin, 0.2% chlorhexidine gluconate versus 2.5% natamycin and voriconazole 1% versus natamycin 5%. The included trials were small and of variable quality. Differences between different regimens were not statistically different, which may reflect the low sample sizes.

Authors' conclusions

Based on the trials included in this review, there is no evidence to date that any particular drug, or combination of drugs, is more effective in the management of fungal keratitis. The trials included in this review were of variable quality and were generally underpowered.

PLAIN LANGUAGE SUMMARY

Medical interventions for fungal infection of the clear front part of the eye (cornea)

Fungal keratitis (fungal infection of the cornea) occurs rarely in higher income countries but is relatively common in lower income countries. If left untreated the cornea may perforate and may lead to blindness. Although there are a number of medications available, it is not clear which is the most effective and cost-effective. This review identified nine randomised controlled trials with 568 participants using different combinations of antifungal drugs. The trials were mainly conducted in India; they were small and of variable quality. Although there were some observed differences, these could have occurred by chance; none of the studies were large enough to determine conclusively which agents work best. Further trials with a larger sample size are required in order to answer this important question.

BACKGROUND

Description of the condition

Fungal infections can involve different parts of the eye and perioocular tissues including the lacrimal apparatus, conjunctiva, eyelids and bony orbit. The most common sites for fungal infections of the eye involve the cornea and the retina or vitreous (O' Brien 1997). In the past few decades there have been increased reports of fungal infections of the eye (O' Day 1996). These can be mainly attributed to increased clinical awareness and improved laboratory techniques and may also have been caused by widespread use of corticosteroids, antibiotics, immunosuppressants, chemotherapeutic drugs and ocular prosthetic devices (O' Brien 1997).

Epidemiology

Fungal keratitis or keratomycosis is relatively uncommon in developed countries. There have been no high quality published reports on the incidence rates of the disease. In the United States, it has been reported that the total number of fungal keratitis cases annually is approximately 1500 (O' Day 1996). It is, however, more common in agricultural and tropical countries. In South Florida, a nine year survey from 1968 to 1977 revealed that 133 out of 633 cases of corneal ulcers were fungal in origin (Liesegang 1980). In the Philippines, a 25 year survey on central microbial keratitis revealed a total of 430 cases (Valenton 2000). The most common etiologic agents are *Fusarium*, *Aspergillus fumigatus* and *Aspergillus flavus*. In Hyderabad, India, a ten year study on fungal keratitis showed 1,352 culture proven cases, the most common etiologic agents included *Fusarium*, *Aspergillus*, and *Curvularia spp* (Gopinathan 2002).

The most common predisposing factor in fungal keratitis is trauma associated with plant material. Other risk factors include long-term corticosteroid use and immuno-compromised patients (O' Day 1996).

Presentation and diagnosis

Fungal infections almost always present in an insidious manner. The infection may be recognised within days or weeks and it is not uncommon for the traumatised epithelium to heal completely before signs of infection appear. During this latent period the patient may be asymptomatic. However, within a few days or weeks the patient might complain of discomfort, photophobia and discharge.

During this period, a persistent infiltrate at the site of previous superficial trauma is present which may increase in size and density in time. The epithelium tends to heal over this inflammatory focus, although there may be recurrent episodes of epithelial breakdown. The cornea becomes slightly thickened and 'satellite' lesions may develop peripheral to the focal area of infiltration.

If not treated, the inflammatory signs gradually progress causing permanent breakdown of the epithelium, stromal ulceration, or formation of descemetocoele (corneal thinning). The cornea may eventually perforate. Neovascularisation may occur as a result of inflammation, which may lead to severe scarring of the cornea. Associated signs indicating the severity of inflammation include the presence of hypopyon (pus in the anterior chamber) and ciliary injection. Fungi can invade the deep stroma with great rapidity

and may gain access to the anterior chamber.
It is important to determine the etiologic agent of the corneal ulcer. Combined infections with bacteria and fungi or even with multiple fungi might occur. Diagnosis is usually achieved by scraping material from the base of the ulcer. Some of this material is stained for fungi and bacteria, the rest is cultured on solid and liquid media. In severe cases where diagnosis is unclear it may be necessary to take a larger corneal biopsy.

Description of the intervention

Management of fungal keratitis is mainly by antifungal agents. Keratoplasty or corneal transplant is usually reserved for acute management of corneal perforation and for visual rehabilitation following corneal scarring.
The number of antifungal agents available for therapy is few compared with the number of pathogens capable of infecting the eye (O' Brien 1997). Current antifungal agents are divided into four groups: polyenes, imidazoles, triazoles and fluorinated pyrimidines. These drugs can be administered topically, intravenously or orally. Topical antifungals can cause toxicity such as punctate keratitis, chemosis recurrent corneal epithelial erosions and conjunctival injection. Sub-conjunctival injections are quite painful and ulceration and necrosis of the conjunctival epithelium may occur.
Current practice in the treatment of fungal keratitis involves the use of topical antifungal drops such as natamycin and topical amphotericin B. Newly discovered triazoles such as voriconazole and posaconazole are also being studied as treatment for fungal keratitis (Galarreta 2007; Tu 2007). In developing countries, where the incidence of fungal keratitis is higher, the costs and availability of these polyene drops may be an issue. Hence, various studies have been performed to validate the effectiveness of chlorhexidine drops as an inexpensive alternative to the treatment of fungal keratitis (Martin 1996). Combination therapy using several antifungal drugs has been studied. The concomitant use of corticosteroids and antifungal agents remains controversial (O' Brien 1997).
In India, due to unavailability and high price of antifungal drugs, different antiseptic agents were studied in vitro and revealed a good dose response for chlorhexidine gluconate while povidone iodone showed a good response in all concentrations (Martin 1996). This initial study was then followed by a randomised controlled trial (RCT) to further determine the clinical effectiveness of chlorhexidine in confirmed fungal keratitis patients (Rahman 1997).

How the intervention might work

Antifungal medications such as the polyenes work by binding to the ergosterol in the cell membrane of the fungal organism. Likewise, imdazoles affect the plasma membrane formation by affecting the ergosterol through microsomal P-450 enzyme. Pyrimidines are transformed to fluorouracil in the cell, therefore blocking the thymidine synthesis (Mabon 1998).

Why it is important to do this review

The gold standard for the treatment of fungal keratitis has not been identified. Due to the low incidence of the disease it is difficult to perform large trials, especially in developed countries. A systematic review of available trials will, therefore, contribute to the evidence base.

OBJECTIVES

To assess the effects of different antifungal drugs in the management of fungal keratitis.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only RCTs in this review.

Types of participants

We included trials where the participants had fungal keratitis diagnosed clinically or microbiologically. We also included trials which included both people with or without corneal perforation, if separate data were available for those without perforation. We excluded studies of participants with mixed bacterial and fungal infections.

Types of interventions

We considered studies using various antifungal drugs in the management of fungal keratitis. This included placebo controlled trials or trials comparing one antifungal agent against another. We also considered trials comparing antifungal drugs with superficial keratectomy.

Types of outcome measures

Primary outcomes

1. Clinical improvement: defined as lessening of pain, decrease in size of infiltrate, disappearance of satellite lesions, rounding

out of feathery margins of the ulcer, disappearance of hypopyon, decrease congestion and healing of epithelium defect. Clinical improvement was assessed on a weekly basis.

2. Clinical cure: defined as healing of the corneal epithelium with scarring of the cornea. Clinical cure was assessed as absence of epithelial defect, absence of cellular reaction in the anterior chamber, presence of corneal vessels and scarring. Clinical cure was usually expected between six to eight weeks. Time to clinical cure was a measured outcome.

Secondary outcomes

1. recurrence;
2. therapeutic success based on the initial size of ulcer;
3. cost-effectiveness of treatment;
4. compliance with treatment;
5. complications: number of participants that experienced complications of fungal keratitis. Complications may include corneal thinning or descemetocoele formation, corneal perforation and endophthalmitis;
6. adverse outcomes as reported in trials. These include: chemosis, punctate keratopathy, recurrent epithelial erosions, conjunctival injections, ulceration and necrosis of conjunctiva, hepatotoxicity and renal toxicity;
7. quality of life.

Follow up

We included trials with at least two months follow up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, Issue 8, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 29 August 2011), MEDLINE (January 1950 to August 2011), EMBASE (January 1980 to August 2011), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to August 2011), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov). There were no language or date restrictions in the search for trials. The electronic databases were last searched on 29 August 2011.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), *m*RCT (Appendix 5) and ClinicalTrials.gov (Appendix 6).

Searching other resources

We searched the reference lists of identified trial reports to find additional trials. We contacted investigators and pharmaceutical companies to identify additional published, unpublished and ongoing studies. We used the Science Citation Index to find studies that have cited the identified trials. We searched conference abstracts for additional studies but journals were not handsearched.

Data collection and analysis

Selection of studies

Titles and abstracts resulting from the searches were reviewed independently by two review authors against the inclusion criteria for the review. We obtained full copies of the studies that definitely or possibly met the inclusion criteria for further assessment on whether the paper should be excluded or included. We contacted trialists for further information in order to determine the relevance of the study.

Data extraction and management

Two review authors extracted details about the methods, participants, interventions, outcomes measured and other details of the included studies and transferred them to the 'Characteristics of included studies' table in RevMan (Review Manager 2011). One review author extracted data using the form developed by the Cochrane Eyes and Vision Group. A second author compared the extraction to the original reports. If data were missing or difficult to determine from a paper, the trialists were approached for clarification and verification. Data were entered into RevMan by one review author, and the second author checked for errors.

Assessment of risk of bias in included studies

Assessment of the risk of bias of studies was undertaken in accordance with the methods given in Chapter 8 the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011). Two review authors independently assessed the studies and disagreements between authors were resolved by discussion. Four bias domains were considered: selection bias, performance bias, detection bias and attrition bias. Assessment was based on the following questions:

1. Selection bias (random sequence generation and allocation concealment): was the sequence of allocation of participants to groups randomly generated and concealed until after treatments were allocated?
2. Performance bias (masking of participants and researchers): were the recipients of care unaware of their assigned treatment? Were persons providing care unaware of the assigned treatment?
3. Detection bias: were persons assessing outcome unaware of the assigned treatment?
4. Attrition bias: were rates of follow up similar in the comparison groups? Was the analysis 'intention-to-treat' (were all participants analysed as randomised)?

We assessed each parameter as 'low risk of bias', 'high risk of bias' or unclear. We contacted trialists for clarification of any parameter graded as unclear. In the protocol we planned to conduct a sensitivity analysis excluding studies at high risk of bias: the current review does not include any meta-analysis so that was not done.

Data synthesis

We presented summary measures for dichotomous data as relative risk ratios. For continuous data we calculated the weighted mean difference. We presented the point estimate and confidence intervals with a 95% confidence interval for individual results.
We did not pool data from the individual trials but in the protocol we specified that we would use the fixed-effect model if the total number of trials in the comparison was three or less provided that heterogeneity had not been detected either statistically or by review. If the number of trials was more than three we planned to use the random-effects model.

Sensitivity analysis

We did not conduct sensitivity analysis as we did not do a meta-analysis. If possible we will do so for future updates so that we can assess how robust the review results were to key decisions and assumptions that were made during the review. Analysis of data will be repeated with the following adjustments:

1. exclusion of studies at greater risk of bias;
2. exclusion of unpublished studies;
3. changing inclusion criteria such as lowering methodological cut-off points.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The electronic searches resulted in 471 reports of possible medical interventions for fungal keratitis. Twenty three abstracts were retrieved in full for further assessment. Six RCTs were identified for inclusion (Agarwal 2001; Mohan 1987; Mohan 1988; Prajna 2003; Rahman 1997; Rahman 1998).
An updated search was done in January 2007 and Februrary 2010. The searches yielded a total 206 and 23 references respectively. The Trials Search Co-ordinator (TSC) scanned the search results for both updates and removed any references which were not relevant to the scope of the review. The update searches did not identify any references which met the inclusion criteria for the review.
A further update search was done in August 2011. After deduplication the search identified a total of 50 references. The TSC scanned the search results and removed 41 references which were not relevant to the scope of the review. We reviewed the remaining nine references of which five were published reports of studies and four were reports of ongoing studies. We assessed the five published reports of studies for potential inclusion in the review. We obtained full-text copies of three studies and have included them in the review (Arora 2011; Mahdy 2010; Prajna 2010). The remaining two reports did not meet the inclusion criteria. Of the four reports of ongoing studies trial NCT00557362 is the initial report of the published paper by Prajna 2010. The three other reports of ongoing studies are relevant to the review and have been added to the studies awaiting assessment section and the results will be included in the review when the studies have been completed (NCT00996736; NCT00997035; NCT00516399).
Contact with first authors of identified trials and searching the reference lists of these studies failed to identify any additional trials. We also approached pharmaceutical companies producing antifungal agents but there was no information on additional trials.

Included studies

See the 'Characteristics of included studies' table for additional details for included studies.

Size of studies

The nine included trials randomised a total of 568 participants: Agarwal 2001 (54 participants); Arora 2011 (30); Mahdy 2010 (48); Mohan 1987 (30) Mohan 1988 (40); Prajna 2003 (116); Prajna 2010 (120); Rahman 1997 (60); Rahman 1998 (70).

Types of participants

Seven of the trials were conducted in India with one trial conducted in Bangladesh (Rahman 1998) and one trial in Egypt (Mahdy 2010). Trials included people with a wide range of ages, from seven to 84 years of age, although in general the patient populations were younger rather than older, with average ages less than 50 years. The majority of the participants were male; the percentage male ranged from 64% to 78% in the included trials.
The majority of the trials included participants with microbiological evidence of fungal keratitis. Two trials (Agarwal 2001; Mahdy 2010) included participants based on a clinical definition only.

Types of interventions

Table 1 summarises the antifungals studied. The trials were heterogenous in terms of types of antifungals studied. Seven antifungal drugs in different preparations and routes of administration

were used. Agarwal 2001 compared topical and systemic itraconazole versus topical itraconazole. Mohan 1987 compared 0.5% and 1% silver sulphadiazine in ointment form to 1% miconazole ointment while Mohan 1988 compared 1% silver sulphadiazine versus 1% miconazole ointment. Prajna 2003 compared 2% econazole and 5% natamycin in topical preparations. Rahman 1997 compared different concentrations of chlorhexidine gluconate versus 5% natamycin while Rahman 1998 compared 0.2% chlorhexidine gluconate versus 2.5% natamycin. Arora 2011 and Prajna 2010 compared topical voriconazole 1% with natamycin 5% and Mahdy 2010 compared amphotericin B combined with subconjunctival injection of fluconazole with amphotericin B alone.
Agarwal 2001, Mohan 1987 and Mohan 1988 were cross-over trials. Data on the first treatment was used for the review.

Types of outcome measures

The majority of trials considered healing of ulcer, or time taken for ulcer to heal, as the primary outcome. Prajna 2010 specified visual acuity as the primary outcome. Follow-up varied: Rahman 1997 and Rahman 1998 considered healing of ulcer at three weeks; Mohan 1987 and Prajna 2003 considered healing at four weeks; Mohan 1988 did not specify a cut-off time but noted healing of ulcers within two to four weeks; Agarwal 2001 considered healing of ulcer at six weeks as primary outcome; Arora 2011 followed up for a minimum of 10 weeks, or until the ulcer healed; Prajna 2010 specified the main outcome at three months; and Mahdy 2010 also followed up for three months. The trials noted a healed ulcer based on slit lamp findings such as disappearance of hypopyon and circumoral congestion, absence of fluorescein staining. Local and systemic adverse reactions were noted by some trials.

Excluded studies

See the 'Characteristics of excluded studies' table for details.

Risk of bias in included studies

See Figure 1 and Figure 2.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

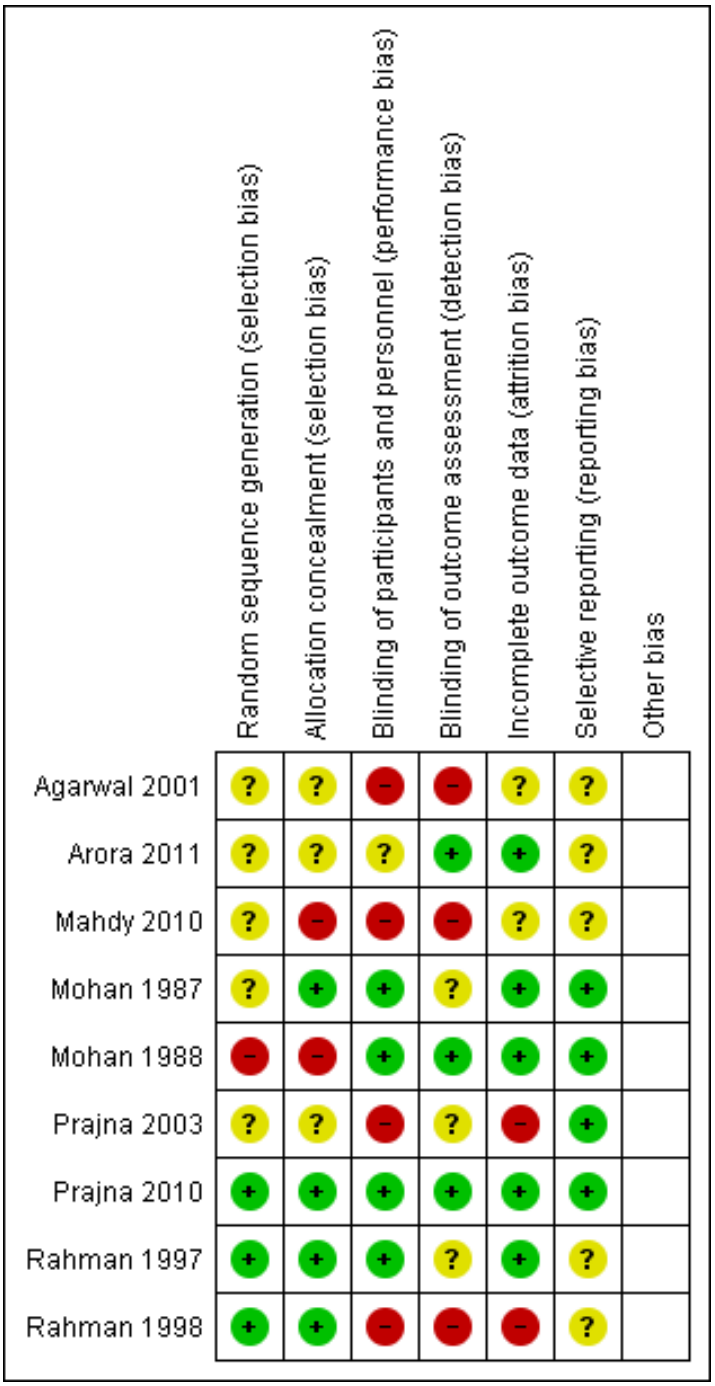
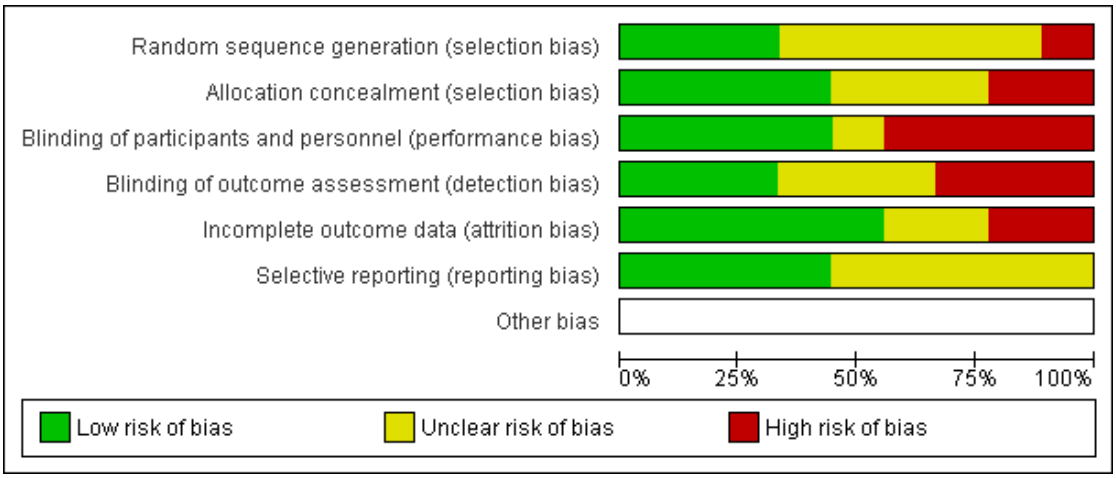


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Only three trials reported adequate methods of sequence generation and allocation concealment (Prajna 2010; Rahman 1997; Rahman 1998).

Blinding

Masking of participants was not always possible. Only Mohan 1988 and Prajna 2010 reported adequate masking of participants, personnel and outcome assessment.

Incomplete outcome data

Arora 2011, Mohan 1987; Mohan 1988, Prajna 2010 and Rahman 1997 had reasonably complete data. In the other studies, attrition bias was considered to be possible.

Selective reporting

Selective reporting was not considered to be a major problem in the included trials but it was not always possible to assess this adequately.

Other potential sources of bias

Trials by Mohan 1987, Mohan 1988 and Agarwal 2001 were cross-over trials which can be a potential source of bias.

Effects of interventions

Treatment failure

1. Topical itraconazole versus topical and systemic itraconazole

The combination of topical (1%) and oral intraconazole (100 mg twice daily for three weeks) did not appear to confer any additional advantage to itraconazole alone (Agarwal 2001) with a relative risk (RR) of 1.0; 95% confidence internal (CI) 0.37 to 2.71.

2. Silver sulphadiazine versus miconazole

The results of two studies by the same author (Mohan 1987; Mohan 1988) indicated that silver sulphadiazine was more effective than miconazole, however, the confidence intervals were wide and the results were also compatible with a greater efficacy of miconazole. Mohan 1987: silver sulphadiazine (0.5% and 1%) compared to 1% miconazole gave a RR (of failure, i.e. not healing of ulcer) of 0.63; 95% CI 0.21 to 1.83. Mohan 1988 1% silver sulphadiazine ointment compared to 1% miconazole ointment: RR 0.44; 95% CI 0.16 to 1.21. The pooled estimate of these two trials was 0.51 (95% CI 0.25, 1.07) (Analysis 1.1).

3. Econazole versus natamycin

In Prajna 2003, there appeared to be little difference in the effects of econazole and natamycin: RR 0.99: 95% CI 0.8 to 1.21.

4. Chlorhexidine gluconate versus natamycin

In two trials by the same investigators (Rahman 1997; Rahman 1998) there was some evidence for a favourable effect of chlorhex-

idine compared to natamycin in response at five days (Analysis 2.1), however, the results on healing of the ulcer at 21 days was less conclusive (Analysis 2.2).

5. Voriconazole versus natamycin

Arora 2011 and Prajna 2010 found no evidence for any difference between these two antifungal agents. However, Arora 2011 was rather small and it was not possible to combine the results of these studies because of differences in outcomes presented. Prajna 2010 found that people treated with voriconazole had a 1 line better best correct visual acuity compared to people treated with natamycin at three months, however, this difference was not statistically significant.

6. Amphotericin B combined with fluconazole (subconjunctival injection)

Mahdy 2010 found a higher proportion of ulcers healed with combination treatment (amphotericin B and fluconazole) (83%) compared to amphotericin alone (67%), however. this study was considered to be at relatively high risk of bias (Figure 1).

Adverse reactions

Mild side effects were noted in topical itraconazole, which included:

1. corneal oedema in two cases;
2. increased intraocular pressure in two cases; and
3. prolonged congestion in four cases.

On the other hand, no significant side effects were reported in patients with oral itraconazole.

Mild local allergic reactions were observed in three eyes using silver sulphadiazine ointment as reported in Mohan 1988.

Prajna 2003 did not elaborate on the ocular and systemic adverse reactions due to 2% econazole and 5% natamycin. No systematic adverse effects were recorded in Prajna 2010. There were nine corneal perforations in the natamycin group and 10 in the voriconazole group. No adverse reactions to study medications were noted in Arora 2011. In Mahdy 2010 two cases of subconjunctival haemorrhage associated with the injection site were noted but no conjunctival necrosis.

There was no report of significant systemic or ocular adverse reactions from both chlorhexidine gluconate and natamycin. A case of temporary punctate epitheliopathy was observed in one participant receiving chlorhexidine gluconate. This was attributed to increased frequency of application of the drops. No early cataract formation was observed at six months to one year after treatment for participants exposed to chlorhexidine gluconate and natamycin.

DISCUSSION

This systematic review aimed to provide a critical, quantitative overview of previous clinical research and to yield, where possible, summary effect measures with increased statistical power by combining multiple small clinical trials. The current review includes nine trials comparing different antifungal drugs in topical drops, ointment and oral preparations for the treatment of fungal keratitis. All trials were done in developing countries since the incidence is higher compared to developed countries such as the United States. There are still no large multicentre randomised trials on the treatment of fungal keratitis.

Seven antifungal agents, namely: voriconazole, econazole, itraconazole, miconazole, natamycin, chlorhexidine gluconate and silver sulphadiazine were studied. The latter two are not part of the conventional drugs which act on the hyphal cell membranes. The use of alternative drugs such as chlorhexidine gluconate and silver sulphadiazine may indicate that conventional drugs are not always available, are expensive and ineffective. Since fungal keratitis is more common in developing countries the use of inexpensive alternative drugs is promising. In addition, a less financial incentive has been offered to pharmaceutical companies to invest in the development of ocular antifungal agents. The only commercially available antifungal drug in the United States in ophthalmic form is natamycin (Natacyn 5% by Alcon Laboratories). In Asia and Africa, Natacyn is given as a service drug but with limited availability. In India, topical natamycin is manufactured by a local pharmaceutical company, however, no clinical trials have been done on this drug.

Three pairs of trials had the same primary author. One pair compared different concentrations of the drug chlorhexidine gluconate with natamycin, while the other pair compared different concentrations of silver sulphadiazine with miconazole. Succeeding studies may have based the concentration of the study drug from the previous trials.The other pair considered different formulations.

Although natamycin was used as the control drug in four of the six trials, it is not yet considered as the gold standard for treatment for fungal ulcer because of low success rate.

Comparing treatment effects of all the drug preparations studied, silver sulphadiazine ointment has the lowest proportion of participants with treatment failure followed by itraconazole in both treatment arms, miconazole ointment, chlorhexidine gluconate, econazole. The drug with the highest failure proportion with failed ulcer was natamycin (2.5% and 5%). However, these comparisons between treatment arms of different studies do not represent randomised comparisons (it is effectively an observational study), thus these differences may reflect differences in the different populations studied.

Summary of main results

Based on the nine trials included in this review, there is no evidence that any particular drug, or combination of drugs, is more effective in the management of fungal keratitis. However, the trials

included in this review were of variable quality and were generally underpowered.

Overall completeness and applicability of evidence

The evidence supporting the treatment of fungal keratitis appears to be weak. Only nine trials of variable quality were identified. The trials considered different preparations and comparisons and so it was not possible usefully to pool the data.
Treatment regimens such as amphotericin B and other new drugs such as voriconazole have not yet been studied in a large scale manner.

Quality of the evidence

The review provides weak evidence for the drugs used in management of fungal keratitis. Nine trials with 568 participants have been included using different antifungal medications. There was no consistent drug of comparison (control). We did not combine results since the drugs used were different.

Potential biases in the review process

An exhaustive search on the trials was done. However, there are few RCTs on fungal keratitis since the disease is rare in developed countries. Since fungal keratitis is more often studied in developing countries, unpublished reports might have been excluded.

Agreements and disagreements with other studies or reviews

Most of the trials on management of fungal keratitis gathered during the literature search are case series. Only the RCTs were included in the review.

AUTHORS' CONCLUSIONS

Implications for practice

The first line of treatment in fungal keratitis is topical antifungal agents. Although it is prudent to wait for culture and sensitivity results before instituting medical therapy, fungi do not grow as fast as bacteria even under well-controlled conditions. Thus, antifungal agents are administered promptly once fungal elements are seen on microbiology examination.

Current antifungal agents used in the treatment of fungal keratitis in the RCTs are varied. Furthermore, the different studies are weak, owing to their small sample size. The results of these studies also did not show a significant difference among the heterogenous interventions. There is little evidence to support the use of any particular drug, or combination of drugs.

Implications for research

There is a need for future multicentre RCTs with a large sample size and the treatment given can be any of the interventions in the previous RCTs. Since the price of these drugs are likewise prohibitive to patients in developing nations, cost-effectiveness of these drugs should also be examined. The search for a cheaper and more effective treatment alternative to what has already been proposed still continues.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Agarwal 2001

Methods	Randomised controlled cross-over trial Masking: It is impossible to be masked due to systemic intervention compared to topical only
Participants	Setting: Calcutta, India 54 patients divided into 2 groups. Group I comprised new patients and Group II comprised patients who had been previously treated with agents. No inclusion and exclusion criteria elaborated. Clinically suspected cases were included Male (69%), 50% aged 21 to 40 years No participants were reported to be excluded or dropped in the study. Patients were followed up for 6 months
Interventions	1% topical itraconazole versus 1% topical itraconazole and 100 mg BID for 3 weeks oral itraconazole. Topical itraconazole was prepared by mixing 100 mg of itraconazole powder with 100 mL artificial tear solution. Oral itraconazole was discontinued after 3 weeks while topical itraconazole was continued for 6 weeks after resolution of keratitis
Outcomes	Main outcome was healing of corneal ulcer, within 6 weeks. Favourable response was further graded based on corneal opacity and visual acuity. Other parameters included residual corneal opacity, best corrected visual acuity and rate of improvement. Side effects such as oedema, glaucoma and congestion were also reported if present
Notes	This is a preliminary study. Aspergillus was common etiology found. Fusarium was not responsive to itraconazole

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"*The patients were divided into two groups*" on the basis of new and untreated patients but no other information is given
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported but treatments different
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported but treatments different

Agarwal 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not possible to assess
Selective reporting (reporting bias)	Unclear risk	Not possible to assess

Arora 2011

Methods	Randomised controlled trial
Participants	Setting: Tertiary care hospital in India 30 people with fungal keratitis, confirmed by microbiology Predominantly male (group A 67% male, group B 73% male). Average age 37.9 (15.1) years in group A and 48.5 (13.5) years in group B
Interventions	5% natamycin versus 1% voriconazole. Patients were followed up for a minimum of 10 weeks, or until complete resolution of the ulcer
Outcomes	Resolution of the ulcer and visual acuity
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*This study was randomized, double-masked, interventional, pilot study of patients with fungal keratitis*". Methods, first paragraph "*They were randomly divided into two groups of 15 patients using the lottery methods*". Methods, first paragraph
Allocation concealment (selection bias)	Unclear risk	"*Double masking of treatment assignment was achieved by dispensing the medications in identical opaque bottles and by having the ward nurses wipe any white residue from the patient's eye prior to study assessment as natamycin is delivered via suspension, whereas VRC is in solution*". Methods, first paragraph
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*Double masking of treatment assignment was achieved by dispensing the medications in identical opaque bottles and by having the ward nurses wipe any white residue from the patient's eye prior to study assessment as natamycin is delivered via suspension, whereas VRC is in solution*". Methods, first paragraph
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Double masking of treatment assignment was achieved by dispensing the medications in identical opaque bottles and by having the ward nurses wipe any white residue from the*

Arora 2011 (*Continued*)

		patient's eye prior to study assessment as natamycin is delivered via suspension, whereas VRC is in solution". Methods, first paragraph
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no reported drop outs in both treatment and control groups. Follow up ranged from 10 days to 60 days
Selective reporting (reporting bias)	Unclear risk	The primary outcome was defined as the "*time taken for the complete resolution of the ulcer*". Methods, last paragraph Various other outcomes reported e.g., visual acuity and mean size of the ulcer

Mahdy 2010

Methods	Randomised controlled trial
Participants	Setting: hospital in Egypt 48 people with clinical signs of fungal keratitis Male (65%), aged 15 to 64 years, average age 44 years
Interventions	Topical amphotericin B (0.5 mg/ml) and subconjunctival fluconazole (2mg/ml) compared to topical amphotericin B alone
Outcomes	Healing of corneal ulcer. Follow-up 3 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*The study is a prospective, randomized one,..."* Page 282 "*Eyes with similar clinical and laboratory findings were classified into 2 groups of treatment.*" Page 282
Allocation concealment (selection bias)	High risk	No description on method of allocation concealment however the study groups were exactly matched for fungal species (table 2) which is unlikely on this number of patients if the allocation was truly random
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not masked

Mahdy 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Difficult to judge from report

Mohan 1987

Methods	Randomised controlled cross-over trial Six ulcers had no response. No significant systemic and ocular side effects noted
Participants	Setting: New Delhi, India Included patients were positive for KOH smear 30 patients were included; 10 for 0.5% silver sulphadiazine, 10 for 1% silver sulphadiazine and 10 for 1% miconazole Age and sex not reported
Interventions	0.5% topical silver sulphadiazine, 1% topical silver sulphadiazine and 1% topical miconazole all in ointment form
Outcomes	Main outcome was healing described as absence of fluorescein staining, disappearance of hypopyon, lack of circumcorneal congestion and negative culture
Notes	Silver sulphadiazine had 100% effectivity in Fusarium ulcers

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*The cases were divided into 3 treatment groups […] on a random basis*" *Page 573*
Allocation concealment (selection bias)	Low risk	"*The drugs […were] coded by the Ocular Pharmacology Laboratory*" *Page 573* "*At the end of the trial, the code was broken and the result analyzed*" *Page 573*
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Each patient was given a coded antifungal ointment tube of 5g to be applied 5 times a day and the entire study was conducted in a double blind manner*" *Page 573*
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*The drugs […were] coded by the Ocular Pharmacology Laboratory*" *Page 573*

Mohan 1987 (*Continued*)

		"*Each patient was given a coded antifungal ointment tube of 5g to be applied 5 times a day and the entire study was conducted in a double blind manner*" *Page 573* "*At the end of the trial, the code was broken and the result analyzed*" *Page 573*
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*There was no fallout from this study on account of poor patient compliance*" *Page 573*
Selective reporting (reporting bias)	Low risk	Probably not a problem as they reported ulcers responding to treatment

Mohan 1988

Methods	Randomised controlled double masked cross-over trial Follow-up not stated but rather average healing time. Forty smear positive patients (20 each) were analysed. No reported cases of lost to follow-up
Participants	Setting: New Delhi, India Included patients were smear positive. No exclusion criteria given Male (78%), aged 14 to 68 years
Interventions	1% topical silver sulphadiazine versus 1% miconazole both in ointment preparations. In absence of improvement in one week, participants were switched to other drug. Interventions were continued for 2 more weeks after healing. Mean days of resolution of ulcers was 20.7 for miconazole and 23.9 for silver sulphadiazine
Outcomes	Healing is described as disappearance of hypopyon and circumcorneal congestion, absence of staining and a negative report for culture. Local and systemic adverse effects were noted
Notes	Ulcers were graded based on size and hypopyon. On cross-over, miconazole resistant fusarium ulcers were healed by silver sulphadiazine. Aspergillus was the most common etiologic agent

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"*The patients were assigned alternately to each of two groups*" *Page 192*
Allocation concealment (selection bias)	High risk	Not reported but as sequence was alternate allocation we have assumed that concealment was not possible

Mohan 1988 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*The two ointments were coded and supplied to the patients in identical packings.*" *Page 192/193* "*At the end of the study the code was broken and the results analyzed*" *Page 193*
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*At the end of the study the code was broken and the results analyzed*" *Page 193*
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*Three patients (two on miconazole and one on silver sulphadiazine) developed local allergic reactions, possibly due to the ointment base. They were excluded from further analysis and do not form part of the study materia*l" *Page 193* Low risk of bias recorded here as this is quite a low proportion with missing data and was distributed between the two groups
Selective reporting (reporting bias)	Low risk	Probably not a problem as reported ulcers responding to treatment

Prajna 2003

Methods	Randomised controlled trial 2 patients were lost to follow up in both groups
Participants	Setting: Aravind, India Included patients with smear and culture positive for fungal infection were included. Other inclusion criteria includes size of ulcer at least 2 mm^2 and not more than 60 mm^2. Excluded were patients who did not consent to study and did not meet inclusion criteria. 116 participants included Male (64%), age range 7 to 84 years, average age 37 (13.8) years
Interventions	2% econazole and 5% natamycin in topical eye drops/ suspension. Atropine sulfate ointment were given to both groups
Outcomes	Main outcome is healed ulcer defined as completely healed epithelial defect with no fluorescein staining, non progression of stromal infiltration
Notes	Follow duration was 4 weeks

Risk of bias

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

Prajna 2003 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"*…subjects were randomized to receive either…*" *Page 1235*
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Since natamycin is available as a suspension, and precipitates in the corneal tissue, it was not possible to mask the investigator to the drugs used on subsequent visits*." *Page 1235*
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Since natamycin is available as a suspension, and precipitates in the corneal tissue, it was not possible to mask the investigator to the drugs used on subsequent visits*." *Page 1235*
Incomplete outcome data (attrition bias) All outcomes	High risk	"*Four of the 116 patients randomized at baseline did not return for further follow-up (Fig 1) and were dropped from the study*." *Page 1236* However this contradicts figure 1 where 5 people lost to follow-up by week 4. Also large numbers of people "exited" the study due to clinical worsening or reaction to drops. By week 4 25/61 in the econazole group and 22/55 of natamycin group remained in the study
Selective reporting (reporting bias)	Low risk	Reported "time to cure" and no indication of any unreported variables

Prajna 2010

Methods	Multicentre double masked randomised controlled trial	
Participants	120 people with fungal keratitis at Aravind Eye Hospital, India Male (66%), average age in each of four study groups ranged from 45 to 50 years	
Interventions	Topical natamycin versus topical voriconazole	
Outcomes	Best spectacle-corrected visual acuity at 3 months. Other outcomes included scar size, perforations	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Prajna 2010 (*Continued*)

Random sequence generation (selection bias)	Low risk	"*This study was a randomized, double-masked, clinical trial of patients with fungal corneal ulcers*." Page 673 *"Patients were block randomized in groups of 4 (using the statistical package R; http: // www.r-project.org) by T.P.*" Page 673
Allocation concealment (selection bias)	Low risk	"*Double-masking of treatment assignment was achieved by dispensing the medications in identical opaque bottles and by having the ward nurses wipe any white residue from the patient's eye prior to study assessment. In addition, patients were no longer receiving treatment at 3 months, the time that the primary outcome of final visual acuity was measured. Only the biostatisticians responsible for the randomization coding and the study pharmacist were unmasked.*" Page 673
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Double-masking of treatment assignment was achieved by dispensing the medications in identical opaque bottles and by having the ward nurses wipe any white residue from the patient's eye prior to study assessment. In addition, patients were no longer receiving treatment at 3 months, the time that the primary outcome of final visual acuity was measured. Only the biostatisticians responsible for the randomization coding and the study pharmacist were unmasked.*" Page 673
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Double-masking of treatment assignment was achieved by dispensing the medications in identical opaque bottles and by having the ward nurses wipe any white residue from the patient's eye prior to study assessment. In addition, patients were no longer receiving treatment at 3 months, the time that the primary outcome of final visual acuity was measured. Only the biostatisticians responsible for the randomization coding and the study pharmacist were unmasked.*" Page 673
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*Efficacy endpoints were analyzed on an intent-to-treat basis for all randomized patients enrolled in the study. The primary analysis included the actual 3-month data when available and last observation carried forward for*

Prajna 2010 (*Continued*)

		missing values." Page 674 "*Sensitivity analyses were also performed in which we separately (1) assigned surgical patients the value 1.7 instead of 1.9, (2) assigned patients with perforation (but no surgery) the value 1.7 or 1.9 (instead of using last observation carried forward), (3) analyzed only patients with complete followup, or (4) used multiple imputation (recursive random partitioning-based hot deck method)"* Page 674 11/120 lost to follow-up but evenly distributed across study groups 2/2/4/3
Selective reporting (reporting bias)	Low risk	"*The primary efficacy endpoint was BSCVA at 3 months in the study eye, using a linear regression model with 3-month logMAR BSCVA as the outcome variable and treatment arm (voriconazole vs natamycin) and enrollment logMAR BSCVA and scraping (yes or no) as covariates.*" Page 674 "*Other prespecified endpoints included BSCVA at 3 weeks, adjusting for enrollment BSCVA, and infiltrate/scar size at 3 weeks and 3 months, adjusting for enrollment infiltrate/scar size.*" Page 674

Rahman 1997

Methods	Randomised controlled double masked trial. Two patients were lost to follow-up after randomisation for unknown reasons. Follow-up was at least 21 days
Participants	Setting: Aravind Eye Hospital in Madurai, India Included patients were smear positive for hyphal elements Excluded were patients with only one eye, patients with diabetes mellitus, polymicrobial infections, those unwilling to participate fully or attend for follow up, children under 1 year of age and perforated ulcers Male (76%), aged 50 years and above (33%)
Interventions	Concentration of chlorhexidine gluconate was varied (0.05%, 0.1% and 0.2%) compared to 5% natamycin. Rescue drugs is given if there is no improvement at 5 days
Outcomes	Outcome measures were response at 5 days, cure by day 21 and toxicity. Favorable response was defined as relief of symptoms, improvement of at least one the following signs of inflammation. Healing at 21 days characterised as intact epithelium, with or without scar formation, but no perforation, anterior staphyloma, no adherent leukoma, no fluorescein staining, no hypopyon and improvement of vision or vision no worse than

	baseline
Notes	Data was also stratified based on severity of ulcers. Twelve patients with severe ulcers were excluded in the analysis of outcome at 21 days since only 1 (from chlorhexidine gluconate 0.05%) had favourable response. Fusarium was the most common etiologic agent cultured

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*The randomization was computer generated by statisticians at Aravind, using the one-sample run test.*" Page 143
Allocation concealment (selection bias)	Low risk	"*… 60 consecutive patients were randomly allocated in a double-masked fashion..*" Page 142 "*The bottles were prepared and labelled only with the randomized numbers by the Aravind executive staff*" Page 143
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"… 60 consecutive patients were randomly allocated in a double-masked fashion.." *Page 142* "*The bottles were prepared and labelled only with the randomized numbers by the Aravind executive staff*" *Page 143*
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*… 60 consecutive patients were randomly allocated in a double-masked fashion..*" Page 142 "*The bottles were prepared and labelled only with the randomized numbers by the Aravind executive staff*" Page 143 But for "treatment failures" the code was broken on day 5 so presumably all assessments after that date were unmasked
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*Two patients were lost to follow-up, so that 58 patients were left in the study*" Page 144
Selective reporting (reporting bias)	Unclear risk	A number of different outcome measures reported and no indication as to whether these were all outcomes on which data collected

Rahman 1998

Methods	Randomised controlled trial with follow up at least 6 months. Seventy one patients were eligible but one was excluded because it was a mixed infection. Seventy patients were randomised to two arms 35 each. Six patients (3 on each arms) were dropped due to incomplete follow-up. Only 32 were assessed at 21 days
Participants	Setting: Bangladesh Included patients where smear positive for hyphal elements. Excluded were patients with only one eye, patients with diabetes mellitus, polymicrobial infections, those unwilling to participate fully or attend for follow up, children under 1 year of age and perforated ulcers Male (74%), aged 50 to 75 years (26%)
Interventions	0.2% chlorhexidine gluconate drops prepared from 20% solution compared to 2.5% natamycin Source of natamycin from the EITC Chittagong. Both drops were given one drop hourly for first 3 hours, then hourly for 2 days, 2 hourly for 5 days, and 3 hourly for 2 weeks - a total of three weeks. No improvement at 5 days was assessed as treatment failure. Rescue drugs were given
Outcomes	Healing at 21 days characterised as intact epithelium, with or without scar formation, but no perforation, anterior staphyloma, no adherent leukoma, no fluorescein staining, no hypopyon and improvement of vision or vision no worse than baseline Divided analysis to smear positive and culture positive cases Toxicity to drug and cataract were also assessed on long term follow-up
Notes	This is a follow-up study done by Rahman. Chlorhexidine gluconate 0.2% was used based on the previous study. Ulcers were graded based on size of ulcer. Classified severe if size is greater than 6 mm. Aspergillus and Fusarium were the two most common etiology

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*The randomization of individuals was computer generated in London....*" Page 920
Allocation concealment (selection bias)	Low risk	"*... and the codes for the alternative treatments sealed in serially numbered opaque envelopes, which were opened in sequence by the research ophthalmologist as the trial progressed.*" Page 920
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*It was not possible to mask the ophthalmologist or nurses to the medications because of their different appearances*" Page 920 Blinding of participants not stated directly but can be inferred that they were masked

Rahman 1998 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	"*It was not possible to mask the ophthalmologist or nurses to the medications because of their different appearances*" Page 920
Incomplete outcome data (attrition bias) All outcomes	High risk	13/35 of chlorhexidine 0.2% group dropped out of the study by 21 days compared to 3/36 of the natamycin 2.5% group. Page 921, figure 1
Selective reporting (reporting bias)	Unclear risk	Main outcome was healing at 21 days of treatment but other follow-up periods also available and not clear that this outcome was pre-specified or not

BID: twice-daily dose
KOH: potassium hydroxide

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

Study	Reason for exclusion
Jones 1975	This is a lecture on the principles in the management of keratomycosis
Kalavathy 2002	The article is a commentary to Agarwal 2001
Kalavathy 2005	This is not a RCT. The first fifty consecutive patients received natamycin while the next fifty patients were given itraconazole
Lavingia 1986	This is an in vitro study on antifungal properties of amphotericin B
Mabon 1998	The article is not a RCT but an overview on fungal keratitis
Mahashabde 1987	This is a case series
Maichuk 1990	This is a case series using antifungal agents for different ocular fungal infections
Maichuk 1991	This is a case series using antifungal agents for different ocular fungal infections
Maichuk 1994	This is a case series using antifungal agents for different ocular fungal infections
Maichuk 1995	This is a case series
Martin 1996	The article is an in vitro study

(*Continued*)

Mitsui 1987	This is a case series
Panda 1996	It is not a RCT. Six consecutive eyes were treated with topical fluconazole
Rao 1997	It is a commentary to another article
Ray 2002	The article is a another commentary to Agarwal 2001
Sun 1996	There was attempt at randomisation. There was no mention of centralised randomisation. Masking of patients was impossible due to different form of the medication given. Masking of care givers and outcome assessors was not reported although difficult to perform because the treatments are in different forms (suspension and oil mixture). There was also no report on drop out rates
Xie 2001	This is a retrospective study on severe fungal ulcers which needed penetrating keratoplasty

RCT: randomised controlled trial

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

NCT00516399

Trial name or title	A Clinical Trial of the Treatment of Fungal Corneal Ulcers With Povidone-Iodine
Methods	Randomised controlled trial
Participants	People with fungal corneal ulcers
Interventions	Povidone-iodine 1.25% ophthalmic solution compared to natamycin ophthalmic suspension, USP 5%
Outcomes	Following text from entry on clinicaltrials.gov: *Number of days until disappearance of hypopyon and criteria for recovery and cure are met and subject is discharged home. Number of treatment failures. Ocular complications from the infection and ocular and systemic complications from the treatment. [Time Frame: Inferior outcome is defined as cure time under povidone-iodine treatment, which is at least 4 days longer than cure time under natamycin, or time until criteria for improvement to hospital discharge is reached.] [Designated as safety issue: Yes]*
Starting date	March 2008
Contact information	Sherwin J Isenberg, M.D. isenberg@ucla.edu
Notes	http://clinicaltrials.gov/ct2/show/NCT00516399 Trial as yet unpublished: completion date September 2011

NCT00996736

Trial name or title	Mycotic Ulcer Treatment Trial I (MUTT I)
Methods	Randomised controlled trial
Participants	People with corneal ulcer aged 16 years and older
Interventions	Natamycin 5% compared to voriconazole 1%
Outcomes	Following text from entry on clinicaltrials.gov: *Primary Outcome Measures: Best spectacle-corrected logMAR visual acuity [Time Frame: 3 months from enrollment] [Designated as safety issue: No]The primary analysis is best spectacle-corrected logMAR visual acuity, correcting for enrollment BSCVA and treatment arm in a multiple linear regression model. The pre-specified non-inferiority margin is less than 1.5 lines logMAR acuity. (Adjusted three-month visual acuity confidence bounds for the difference between the voriconazole and natamycin groups which meet or exceed 0.15 logMAR units would not permit noninferiority to be declared.) Note that this design also allows declaration of superiority (2-sided alpha of 0.05, corrected for an interim analysis)* *Secondary Outcome Measures: Best spectacle-corrected logMAR visual acuity [Time Frame: 3 weeks after enrollment] [Designated as safety issue: No]Best spectacle-corrected logMAR visual acuity at 3 weeks after enrollment, adjusting for enrollment BSCVA and treatment arm in a multiple linear regression model* *Best spectacle-corrected logMAR visual acuity only in Indian sites [Time Frame: 3 weeks and 3 months after enrollment] [Designated as safety issue: No]Best spectacle-corrected logMAR visual acuity only in Indian sites, 3 weeks and 3 months after enrollment, adjusting for enrollment BSCVA and treatment arm in a multiple linear regression model* *Hard contact-lens corrected visual acuity measured in logMAR [Time Frame: 3 months after enrollment] [Designated as safety issue: No]Hard contact-lens corrected visual acuity measured in logMAR 3 months after enrollment* *Size of infiltrate/scar [Time Frame: 3 weeks and 3 months after enrollment] [Designated as safety issue: No]Size of infiltrate/scar at 3 weeks and 3 months after enrollment, using enrollment infiltrate scar/size as a covariate* *Time to resolution of epithelial defect [Time Frame: At the time of resolution of epithelial defect] [Designated as safety issue: No]Time to resolution of epithelial defect* *Number of perforations and other adverse events [Time Frame: At the time of perforation/adverse event] [Designated as safety issue: No]* *Minimum inhibitory concentration of isolates [Time Frame: 3 months after enrollment] [Designated as safety issue: No]* *Microbiological cure at 7 days [Time Frame: 7 days after enrollment] [Designated as safety issue: No]*
Starting date	April 2010
Contact information	Tom Lietman, MD tom.lietman@ucsf.edu
Notes	http://clinicaltrials.gov/ct2/show/NCT00996736

NCT00997035

Trial name or title	Mycotic Ulcer Treatment Trial II (MUTT II)
Methods	Randomised controlled trial
Participants	People aged 16 years or older with fungal corneal ulcer
Interventions	Topical voriconazole 1% combined with oral voriconazole compared to topical voriconazole 1% alone
Outcomes	Following text from entry on clinicaltrials.gov: *Primary Outcome Measures: Rate of perforation [Time Frame: 3 months from enrollment] [Designated as safety issue: No]Comparison of rate of perforation between the treatment groups (topical voriconazole with oral voriconazole vs. topical voriconazole with oral placebo)* *Secondary Outcome Measures: Best spectacle-corrected logMAR visual acuity [Time Frame: 3 weeks after enrollment] [Designated as safety issue: No]Best spectacle-corrected logMAR visual acuity at 3 weeks after enrollment, adjusting for enrollment BSCVA and treatment arm in a multiple linear* *Best spectacle-corrected logMAR visual acuity only in Indian sites [Time Frame: 3 weeks and 3 months after enrollment] [Designated as safety issue: No]Best spectacle-corrected logMAR visual acuity only in Indian sites, 3 weeks and 3 months after enrollment, adjusting for enrollment BSCVA and treatment arm in a multiple linear regression model* *Best spectacle-corrected logMAR visual acuity [Time Frame: 3 months after enrollment] [Designated as safety issue: No]Best spectacle-corrected logMAR visual acuity 3 months after enrollment, adjusting for enrollment BSCVA and treatment arm in a multiple linear* *Hard contact-lens corrected visual acuity measured in logMAR [Time Frame: 3 months after enrollment] [Designated as safety issue: No]Hard contact-lens corrected visual acuity measured in logMAR 3 months after enrollment* *Size of infiltrate/scar [Time Frame: 3 weeks and 3 months after enrollment] [Designated as safety issue: No]Size of infiltrate/scar at 3 weeks and 3 months after enrollment, using enrollment infiltrate scar/size as a covariate* *Time to resolution of epithelial defect [Time Frame: At the time of resolution of epithelial defect] [Designated as safety issue: No]* *Number of adverse events [Time Frame: At the time of adverse event] [Designated as safety issue: No]* *Minimum inhibitory concentration of isolates [Time Frame: 3 months after enrollment] [Designated as safety issue: No]* *Microbiological cure at 7 days [Time Frame: 7 days after enrollment] [Designated as safety issue: No]*
Starting date	May 2010
Contact information	Nisha Acharya, MD, MS nisha.acharya@ucsf.edu
Notes	http://clinicaltrials.gov/ct2/show/NCT00997035

DATA AND ANALYSES

Comparison 1. 1% silver sulphadiazine versus 1% miconazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ulcer healed at 2 to 4 weeks	2	70	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.25, 1.07]

Comparison 2. Chlorhexidine versus natamycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Favourable response at 5 days	2	128	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.28, 0.77]
2 Ulcer healed at 21 days	2	110	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.55, 1.08]

Analysis 1.1. Comparison 1 1% silver sulphadiazine versus 1% miconazole, Outcome 1 Ulcer healed at 2 to 4 weeks.

Review: Medical interventions for fungal keratitis

Comparison: 1 1% silver sulphadiazine versus 1% miconazole

Outcome: 1 Ulcer healed at 2 to 4 weeks

Study or subgroup	Silver sulphadiazine n/N	Miconazole n/N	Risk Ratio(Non-event) M-H,Fixed,95% CI	Weight	Risk Ratio(Non-event) M-H,Fixed,95% CI
Mohan 1987	15/20	6/10		37.2 %	0.63 [0.21, 1.83]
Mohan 1988	16/20	11/20		62.8 %	0.44 [0.16, 1.21]
Total (95% CI)	**40**	**30**		**100.0 %**	**0.51 [0.25, 1.07]**
Total events: 31 (Silver sulphadiazine), 17 (Miconazole)					
Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 1.79 (P = 0.073)					
Test for subgroup differences: Not applicable					

Analysis 2.1. Comparison 2 Chlorhexidine versus natamycin, Outcome 1 Favourable response at 5 days.

Review: Medical interventions for fungal keratitis

Comparison: 2 Chlorhexidine versus natamycin

Outcome: 1 Favourable response at 5 days

Study or subgroup	Chlorhexidine n/N	Natamycin n/N	Risk Ratio(Non-event) M-H,Fixed,95% CI	Weight	Risk Ratio(Non-event) M-H,Fixed,95% CI
Rahman 1997	24/42	7/16		43.4 %	0.76 [0.44, 1.33]
Rahman 1998	31/35	18/35		56.6 %	0.24 [0.09, 0.63]
Total (95% CI)	**77**	**51**		**100.0 %**	**0.46 [0.28, 0.77]**

Total events: 55 (Chlorhexidine), 25 (Natamycin)

Heterogeneity: Chi^2 = 4.90, df = 1 (P = 0.03); I^2 =80%

Test for overall effect: Z = 3.00 (P = 0.0027)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Chlorhexidine versus natamycin, Outcome 2 Ulcer healed at 21 days.

Review: Medical interventions for fungal keratitis

Comparison: 2 Chlorhexidine versus natamycin

Outcome: 2 Ulcer healed at 21 days

Study or subgroup	Chlorhexidine n/N	Natamycin n/N	Risk Ratio(Non-event) M-H,Fixed,95% CI	Weight	Risk Ratio(Non-event) M-H,Fixed,95% CI
Rahman 1997	20/32	7/14		29.7 %	0.75 [0.38, 1.49]
Rahman 1998	14/32	9/32		70.3 %	0.78 [0.54, 1.14]
Total (95% CI)	**64**	**46**		**100.0 %**	**0.77 [0.55, 1.08]**

Total events: 34 (Chlorhexidine), 16 (Natamycin)

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%

Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Anti-fungal agents studied in the included trials

Study	Intervention	Dose	Treatment duration	Intervention	Dose	Treatment duration
Agarwal 2001	Topical itraconazole	1%, every hour	For 6 weeks after keratitis resolved	Oral Itraconazole Topical itraconazole	100 mg twice daily 1%, every hour	3 weeks For 6 weeks after keratitis resolved
Arora 2011	Topical natamycin	5%, every hour	Two weeks "*Further dosage titrated according to the patient's response*"	Topical voriconazole	1%. every hour	Two weeks "*Further dosage titrated according to the patient's response*"
Mahdy 2010	Topical amphotericin B Subconjunctival injection of fluconazole	0.05%, every two hours 0.5 ml of 2 mg/ml, daily	? 20 injections, first 10 every day, second 10 every two days	Topical amphotericin B	0.05%, every two hours	?
Mohan 1987	Topical silver sulphadiazine	Two doses studied: 0.5% and 1%, applied 5 times a day	?	Topical miconazole	1%, applied 5 times a day	?
Mohan 1988	Topical silver sulphadiazine	1%, applied 5 times a day	If no improvement after 1 week, switched to other treatment, treatment continued for 2 weeks after clinical healing of ulcer	Topical miconazole	1%, applied 5 times a day	If no improvement after 1 week, switched to other treatment, treatment continued for 2 weeks after clinical healing of ulcer
Prajna 2003	Topical natamycin	5%, every hour between 7am and 9pm	Four weeks	Topical econazole	2%, every hour between 7am and 9pm	Four weeks
Prajna 2010*	Topical natamycin	5%, every hour while awake	Every hour for one week followed by every two hours	Topical voriconazole	1%, every hour while awake	Every hour for one week followed by every two hours

Table 1. Anti-fungal agents studied in the included trials (*Continued*)

			for two weeks, further continuation at discretion of physician			for two weeks, further continuation at discretion of physician
Rahman 1997	Topical natamycin	5%	Day 1: Half-hourly for three hours, hourly during waking hours for rest of day Days 2 to 5: 2-hourly Then 3-hourly for a further 2 weeks. If no improvement at 5 days swopped to another treatment	Topical chlorhexidine gluconate	Three doses studied: 0.05%, 0.1% and 0.2%	Day 1: Half-hourly for three hours, hourly during waking hours for rest of day Days 2 to 5: 2-hourly Then 3-hourly for a further 2 weeksIf no improvement at 5 days swopped to another treatment
Rahman 1998	Topical natamycin	2.5%	Half-hourly for first 3 hours, then 1 hourly for 2 days, 2 hourly for 5 days, and 3 hourly for 3 weeks. If no improvement at 5 days treatment changed	Topical chlorhexidine gluconate	0.2%	Half-hourly for first 3 hours, then 1 hourly for 2 days, 2 hourly for 5 days, and 3 hourly for 3 weeks. If no improvement at 5 days treatment changed

* Participants were also randomized to "scraping of the corneal epithelium"

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Eye Infections, Fungal
#2 MeSH descriptor Keratitis
#3 fung* near keratit*
#4 fung* near infect* near eye*
#5 fung* near infect* near ocular
#6 keratomycosis
#7 keratomicosis
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Antifungal Agents
#10 MeSH descriptor Natamycin
#11 natamycin*
#12 MeSH descriptor Chlorhexidine
#13 chlorhexidine*
#14 MeSH descriptor Econazole
#15 econazole*
#16 MeSH descriptor Itraconazole
#17 itraconazole*
#18 MeSH descriptor Miconazole
#19 miconazole*
#20 anti fung*
#21 antifung*
#22 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)
#23 (#8 AND #22)

Appendix 2. MEDLINE (OVID) search strategy

1 randomized controlled trial.pt.
2 (randomized or randomised).ab,ti.
3 placebo.ab,ti.
4 dt.fs.
5 randomly.ab,ti.
6 trial.ab,ti.
7 groups.ab,ti.
8 or/1-7
9 exp animals/
10 exp humans/
11 9 not (9 and 10)
12 8 not 11
13 exp eye infections, fungal/
14 exp keratitis/
15 (fung$ adj2 keratit$).tw.
16 (fung$ adj3 infect$ adj3 eye$).tw.
17 (fung$ adj3 infect$ adj3 ocular).tw.
18 keratom?cosis.tw.
19 or/13-18
20 exp antifungal agents/
21 exp natamycin/
22 natamycin$.tw.
23 exp chlorhexidine/

24 chlorhexidine$.tw.
25 exp econazole/
26 econazole$.tw.
27 exp itraconazole/
28 itraconazole$.tw.
29 exp miconazole/
30 miconazole$.tw.
31 antifung$.tw.
32 anti fung$.tw.
33 or/20-32
34 19 and 33
35 12 and 34
The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE (OVID) search strategy

1 exp randomized controlled trial/
2 exp randomization/
3 exp double blind procedure/
4 exp single blind procedure/
5 random$.tw.
6 or/1-5
7 (animal or animal experiment).sh.
8 human.sh.
9 7 and 8
10 7 not 9
11 6 not 10
12 exp clinical trial/
13 (clin$ adj3 trial$).tw.
14 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15 exp placebo/
16 placebo$.tw.
17 random$.tw.
18 exp experimental design/
19 exp crossover procedure/
20 exp control group/
21 exp latin square design/
22 or/12-21
23 22 not 10
24 23 not 11
25 exp comparative study/
26 exp evaluation/
27 exp prospective study/
28 (control$ or prospectiv$ or volunteer$).tw.
29 or/25-28
30 29 not 10 (930488)
31 30 not (11 or 23)
32 11 or 24 or 31
33 exp keratomycosis/
34 exp keratitis/
35 (fung$ adj2 keratit$).tw.
36 (fung$ adj3 infect$ adj3 eye$).tw.

37 (fung$ adj3 infect$ adj3 ocular).tw.
38 keratom?cosis.tw.
39 or/33-38
40 exp antifungal agent/
41 exp natamycin/
42 natamycin$.tw.
43 exp chlorhexidine/
44 chlorhexidine$.tw.
45 exp econazole/
46 econazole$.tw.
47 exp itraconazole/
48 itraconazole$.tw.
49 exp miconazole/
50 miconazole$.tw.
51 antifung$.tw.
52 anti fung$.tw.
53 or/40-52
54 39 and 53
55 32 and 54

Appendix 4. LILACS search strategy

eye$ or ocular and fungal keratitis or keratomycosis

Appendix 5. *meta*Register of Controlled Trials search strategy

fungal keratitis

Appendix 6. ClinicalTrials. gov search strategy

fungal keratitis

WHAT'S NEW

Last assessed as up-to-date: 29 August 2011.

Date	Event	Description
15 December 2011	New citation required but conclusions have not changed	Issue 2, 2012: Three new trials were included in the update (Arora 2011; Mahdy 2010; Prajna 2010).
15 December 2011	New search has been performed	Issue 2, 2012: Electronic searches were updated, risk of bias tables have been completed for all included trials and text modified. A new author joined the review team to help with updating the review

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 1, 2008

Date	Event	Description
22 October 2008	Amended	Converted to new review format.
13 November 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

NVF conceived the review question, co-ordinated the review, organised retrieval of full text copies, wrote to authors of papers for additional information, provided additional data about papers, obtained and screened data on unpublished studies, analysed and interpreted data, performed previous work that was the foundation of the review and wrote the review.

NVF and IP screened initial search results, screened retrieved papers against inclusion criteria, extracted and entered data in to RevMan.

Update Issue 2, 2012

NVF and JE screened search results, appraised quality of papers, extracted and entered data in to RevMan and wrote the update.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- NIHR/Department of Health, UK.

Funded JE to assist in updating the version published in Issue 2, 2012.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antifungal Agents [*therapeutic use]; Eye Infections, Fungal [*drug therapy]; Keratitis [*drug therapy; microbiology]; Randomized Controlled Trials as Topic

MeSH check words

Humans