Review

Linking evidence to treatment for denture stomatitis: A meta-analysis of randomized controlled trials

Elham Emami a,*, Marla Kabawat a, Pierre H. Rompre b, Jocelyne S. Feine c

a Département de Dentisterie et de Restauration, Faculté de Médecine Dentaire, Université de Montréal, Montreal, Canada
b Département de Stomatologie, Faculté de Médecine Dentaire, Université de Montréal, Montreal, Canada
c Oral Health and Society Research Unit, Faculty of Dentistry; Department of Epidemiology and Biostatistics and Department of Oncology, Faculty of Medicine, McGill University, Montreal, Quebec, Canada

A B S T R A C T

Objectives: The aim of this meta-analysis was to compare the efficacy of antifungal therapy with any other alternative methods used for the treatment of denture stomatitis.

Data sources: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews were searched, complemented by hand searching, until the first week of January 2013.

Study selection: Included studies consisted of randomized clinical trials published in English or French, which compared antifungals with any other alternative or placebo, used for the treatment of denture stomatitis. The remission of clinical signs of denture stomatitis, and the reduction in Candida colony counts were considered as the clinical and microbiological outcomes, respectively. Random effects models were used to conduct the statistical analyses.

Results: From 233 identified articles, a total of 15 manuscripts on 14 randomized controlled trials were included in systematic review and 8 in the meta-analysis. No statistically significant difference between antifungal treatment and disinfection methods was found for both clinical (OR = 0.7; 95% CI: 0.32–1.36; Z = −1.14; p = 0.256) and microbiological (OR = 0.8; 95% CI: 0.26–2.5; Z = −0.35; p = 0.724) outcomes. The meta-analysis showed a statistically significant difference between an antifungal and a placebo for the microbiological outcome (OR = 0.32; 95% CI: 0.12–0.89; Z = −2.2; p = 0.028), favouring the antifungals. However, there was no statistically significant difference between antifungal and placebo for the clinical outcome (OR = 0.2; 95% CI: 0.04–1.04; Z = −1.9; p = 0.056).

Conclusions: Disinfection agents, antiseptic mouthwashes, natural substances with antimicrobial properties, microwave disinfection and photodynamic therapy could be suggested as an adjunct or alternative to antifungal medications in the treatment of denture stomatitis.

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1. **Introduction**

Denture-related erythematous stomatitis (denture stomatitis), a chronic inflammatory response of the palatal mucosa to a harmful stimuli, is widespread in edentate individuals and is considered to be the determinant of oral health in this population.\(^1\) It is also the most common mucosal lesion associated with removable prostheses,\(^2\)\(^3\) affecting one in every three complete denture wearers.\(^4\) Several risk factors have been reported to be associated with denture stomatitis, including trauma,\(^5\) poor hygienic habits, continuous and nocturnal denture wear \(^6\) and fungal infections (particularly *Candida albicans*).\(^7\)

Antifungal medications are routinely used by clinicians for the management of this condition, based on some evidence that *Candida* is the main etiological factor in the onset of denture stomatitis.\(^8\)\(^9\)\(^10\) However, a cause-and-effect relationship has never been shown, and some studies did not demonstrate an association between the presence of denture stomatitis and the presence of *Candida* infection.\(^12\)\(^13\)\(^14\) Furthermore, high recurrence rates of denture-related erythematous stomatitis and re-colonization of *Candida* after the cessation of antifungal treatment have been reported.\(^15\)\(^16\)\(^17\)

A meta-analysis of randomized controlled trials comparing the efficacy of antifungal therapies with other alternatives approaches and placebo will shed a light on the efficacy of these treatments and will guide the development of clinical practice guidelines.\(^19\) These guidelines are needed in order to direct the healthcare professional in treatment decision-making.

We tested the null hypothesis that there is no difference between antifungals and other alternatives in the treatment of denture stomatitis.

2. **Material and methods**

This systematic review and meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.\(^19\)

2.1. **Search strategy and eligibility criteria**

The following databases were used for the identification of studies: MEDLINE via OVID (1946 to January Week 1 2013), EMBASE (1996 to 2013 Week 02), Cochrane Central Register of Controlled Trials (until December 2012) and the Cochrane Database of Systematic Reviews (2005 to November 2012). We included all relevant randomized controlled trials that compared the efficacy of antifungal medications with other methods used in the treatment of denture-related erythematous stomatitis in adults wearing conventional acrylic removable complete dentures. Trials with a period of treatment of 7 days or less and quasi-experimental randomized trials were excluded.

An adapted search strategy for MEDLINE and EMBASE from a Cochrane systematic review protocol was used \(^20\) (Appendix 1). The search was complemented by manual search of reference lists. No language restriction was considered. Titles and abstracts of the identified articles were screened independently by two reviewers. Full text articles were obtained for studies that appear to meet the inclusion criteria and were reassessed independently by three reviewers. Any disagreement was discussed and resolved by consensus. The study flow chart is depicted in Fig. 1.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdent.2013.11.021.

2.2. **Data extraction and outcomes**

The data collected from each study included the following: authors, year and country of the study, study design, population characteristics, intervention characteristics, type of measurement instrument and main outcomes (clinical and microbiological outcomes). The remission of clinical signs and severity of denture stomatitis were considered as the clinical outcome, while reduction in the level of *Candida* colony counts (CFUs) was used as the microbiological outcome.

2.3. **Assessment of the methodological quality**

The quality of included studies was assessed following the Cochrane Handbook for Systematic Reviews of Interventions.\(^21\) This assessment included the following parameters: sequence generation, allocation concealment, blinding of care providers and participants, masking outcome assessors, reference to withdrawals or dropouts and intention-to-treat analysis (ITT). We graded each parameter of trial methodological quality as: ‘adequate’, ‘inadequate’ and ‘unclear or not reported’.

2.4. **Statistical analysis**

All analyses were performed using Comprehensive Meta-Analysis, Version 2 (Biostat\(^\text{TM}\)) software. Only studies of similar comparisons reporting the same outcome measures were included in the meta-analysis.

Odds Ratios (OR) and 95% Confidence Interval (CI) were calculated to compare results across studies. Heterogeneity between studies was assessed by the Cochrane Q test and I\(^2\). A *p*-value ≤ 0.20 and I\(^2\) of at least 50% were taken as indicators of heterogeneity between trials. A-Priori subgroup analysis was planned and random effect model were used to conduct the analyses. This approach accounted for inter-study variations and provided more conservative estimate comparing to a fixed model.\(^24\) Due to the small number of studies within subgroups, a pooled estimate of tau-squared in a random-effects meta-analysis was given. A forest plot was used to show the point estimate of the results of each individual study and the pooled estimate for subgroups (antifungal vs. disinfection method and antifungal vs. placebo). The overall effect was not presented because a difference between the subgroups was expected (Figs. 2 and 3).

3. **Results**

3.1. **Characteristics of studies**

A total of 233 articles were identified. After duplicates elimination, 187 articles were searched by title and abstract. Only 24 were eligible for full-text searching (Fig. 1: flow chart).
All the studies were published in English. Of these, 9 were eliminated because they did not meet the inclusion criteria or because they used outcomes beyond the scope of this review. Two manuscripts reported on the same population with different outcomes of interest in each publication. Thus, a total of 15 manuscripts on 14 randomized controlled trials were included in the review. From a total of 14 RCTs, only 8 studies with comparable clinical and microbiological outcomes were included in the meta-analysis. Accordingly, the remission of clinical sign of denture stomatitis and positive cultures of Candida from the palatal mucosa were considered as outcomes for the meta-analysis. The earliest study was conducted in 1975 and the most recent in 2012. The sample sizes varied from 24 to 100 participants and the age range of participants was between 19 and 91 years. Participants were recruited from dental clinics of various universities from a public health centre.

Fig. 1 – Systematic review flow diagram.

![Flow diagram](image)

Fig. 2 – Meta-analysis comparing antifungal with alternative treatment regarding the clinical outcome. 1, extract of Melaleuca alternifolia; 2, photodynamic therapy; 3, microwave; 4, extract of Punica granatum; †, placebo heat-denatured lozenges.
Fig. 3 – Meta-analysis comparing antifungal with alternative treatment regarding the microbiological outcome. 1, Hexetidine; 2, extract of Punica granatum; †, placebo suspension in a tissue conditioner; ‡, placebo heat-denatured lozenges; *, placebo oral adhesive.

The diagnosis of denture stomatitis was based on direct observation of the palatal mucosa or photographs of the palate. Different classifications and scales of inflammation were used to categorize different types of denture stomatitis. The majority of the studies investigated both clinical and microbiological outcomes. Only two manuscripts reported on one of these outcomes.

In most trials, oral biofilm was collected by taking a sample from the palatal tissue or the internal surface of the denture. Various mediums were used for microbiological cultures. Some studies also used cultures of saliva samples and smears for microscopic investigations.

More details on the characteristics of each study are outlined in Appendix 2.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdent.2013.11.021.

3.2. Methodological quality of the trials

A summary of the quality of the included trials, based on sequence generation, allocation concealment, blinding and reports on withdrawals and dropouts, is presented in Table 1.

Table 1 – Methodological quality summary.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Adequate sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of care providers/participants</th>
<th>Blinding of outcome assessors</th>
<th>Report on withdrawals and dropouts</th>
</tr>
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* Row includes trials with multiple publications on the same population reporting on different outcomes.
Only three trials reported the methods of randomized sequence generation and concealment of allocation. The others simply stated that the selection was made randomly. Some trials reported blinding of the participants or the care providers and masking the outcome assessors. Most trials did not report on dropouts and withdrawals, except for three. No trial used intention-to-treat analyses.

3.3. Effect of interventions

A summary of the retrieved information from the studies included in the review are presented below and in Appendix 2. To facilitate the comparison, disinfection agents, antiseptic mouthwashes, natural substances with antimicrobial properties, microwave disinfection and photodynamic therapy were all grouped as disinfection methods.

3.4. Disinfection method versus antifungal medication

When chlorhexidine digluconate was compared to amphotericin B, they were both effective in regard to the clinical and microbiological outcomes. Recurrence of disease was reported 14 days after the discontinuation of both treatments. In addition, there was no difference between the use of Listerine mouthwash (composition: menthol, thymol, methyl salicylate and eucalyptol) and a nystatin oral suspension or between hexetidene mouthrinse and fluconazole capsules. When considering natural substances, the incorporation of essential oil Melaleuca alternifolia or nystatin in a tissue conditioner showed similar positive effect, with no statistically significant difference between treatments (p ≥ 0.05). Likewise, the essential oil Zataria multiflora was clinically as effective as miconazole 2% gel, but slightly less effective in the reduction of Candida colony number. Relapse occurred for both treatments after 2 weeks of discontinuation of treatment. Comparison of the extract of Punica granatum with miconazole gel showed that miconazole was slightly more effective in reducing the erythema associated with denture stomatitis (p ≤ 0.01). However, there was no statistically significant difference between treatments regarding the microbiological outcome (p > 0.01). Finally, in one recent trial, both nystatin mouthwash and garlic aqueous solution resulted in statistically significant reduction in the extent of the erythema (p < 0.0001).

Neppelenbroek et al. evaluated the use of microwaves as a disinfection method. They found that the use of microwave alone and microwave combined with topical application of miconazole, had similar results in regard to the reduction of the palatal inflammation. The antifungal used alone or oral hygiene instructions were not effective either in reducing the clinical signs of denture stomatitis or the number of Candida colonies. In the study by Sanita et al., microwaves were as effective as topical nystatin in the treatment of denture stomatitis in a diabetic population. Finally, the use of photodynamic therapy, as a means of disinfection of the palate and the denture, had the same efficacy as nystatin suspension. In these previous studies, similar recurrence of denture stomatitis was reported after cessation of the antifungal medications, the use of the microwave and photodynamic therapy.

When comparable data were pooled in the meta-analysis, no statistically significant difference between disinfection methods and antifungal treatment was found for both clinical (OR = 0.7; 95% CI: 0.32–1.36; Z = −1.14; p = 0.256) and microbiological (OR = 0.8; 95% CI: 0.26–2.5; Z = −0.35; p = 0.724) outcomes. There was no evidence of heterogeneity between trials for both outcomes (Chi² = 2.256, df = 3, p = 0.521; I² = 0.0%; and Chi² = 0.225, df = 1, p = 0.635, I² = 0.0%, for the clinical and microbiological outcomes respectively) (Figs. 2 and 3).

3.5. Antifungal medication versus placebo

When amphotericin was incorporated into a denture adhesive, it had the same efficacy as a placebo adhesive in improving the clinical and microbiological outcomes. Furthermore, when a tissue conditioner containing a 2.5% Pimafucin suspension was compared to a placebo tissue conditioner, no statistically significant difference was found in regard to the clinical signs of denture stomatitis (p ≥ 0.05). In contrast, amphotericin B lozenges and nystatin lozenges were more effective than placebo lozenges. Similarly, when fluconazole capsules were compared to placebo capsules, inflammation and yeast scores were reduced in the treatment group only. However, at 4 weeks follow-up, there was no difference between group due to clinical and microbiological relapse.

The meta-analysis showed a statistically significant difference between an antifungal and a placebo for the microbiological outcome (OR = 0.32; 95% CI: 0.12–0.89; Z = −2.2; p = 0.028), favouring the antifungals. However, some heterogeneity between trials was observed (Chi² = 3.85, df = 2, p = 0.146; I² = 48%) (Fig. 3). In contrast, there was no statistically significant difference between antifungal and placebo for the clinical outcome (OR = 0.2; 95% CI: 0.04–1.04; Z = −1.9; p = 0.056). However, only one study was included in this analysis (Fig. 2).

4. Discussion

To our knowledge, this is the first meta-analysis that compares the efficacy of antifungals with alternative methods such as disinfection agents, antiseptic mouthwashes, natural substances with antimicrobial properties, microwave disinfection, and photodynamic therapy, in the treatment of denture stomatitis.

The findings of this meta-analysis suggest that disinfection and antiseptic methods could be as effective as antifungal therapy in the treatment of denture-related erythematous stomatitis. Our findings support the results of several studies that showed Listerine, chlorhexidine and hexetidine, as well as microwave irradiation, photodynamic therapy and natural herbal substances, display antimicrobial and antifungal activities which could explain the positive outcomes obtained in the treatment of denture stomatitis.

Surprisingly, we found conflicting results when antifungals were compared to placebos, such as tissue conditioner, denture adhesive or placebo medication. The tissue conditioner and
the denture adhesive were found to be as effective as amphotericin and pimafucin, especially in the reduction of the palatal erythema. However, antifungal medications were more effective when placebo lozenges and capsules were used. The clinical efficacy of the oral adhesive and the tissue conditioner could be explained by their cushioning effect on the palatal mucosa, which reduces the denture trauma and thus, leads to a reduction in the inflammation.

According to the literature, the combination of antifungal therapy, disinfection of the denture, removal of the dentures at night, as well as adjustment, relining and remaking of the prosthesis could be used in the treatment of denture stomatitis. The improvement of oral and prosthetic hygiene reduces the formation of a denture biofilm, and prosthesis adjustments reduce the traumatic stress to surrounding tissues. In this review, removal of the dentures at night was considered among the specific denture hygiene instructions received by the studies’ participants. Several studies indicated that nocturnal denture wear plays a role in the aetiology of denture stomatitis. Nocturnal and continuous prosthesis wear could reduce the protective effect of saliva, decrease the cleaning effect of the tongue, prevent proper oxygenation of the palatal mucosa and, finally, increase local trauma to the mucosa. These effects make denture wearers more prone to mucosal mechanical and microbiological injuries and, therefore, increase the risk of denture stomatitis in this population. Thus, clinicians should suggest that their patients should remove their prosthesis at night and avoid continuous denture wear, if possible.

Since disinfection methods could have the same efficacy as antifungal medications, the use of antifungal treatments can be postponed until microbiological analyses confirm the presence of associated candidiasis. The conservative approach involving disinfection methods could avoid the overuse of antifungals which could have side effects such as gastrointestinal disturbances, hypersensitivity, renal and liver toxicity and interaction with other medicines. In addition, the extensive use of antifungal medications can lead to the development of microbial resistance. Another predicament of antifungals is the high recurrence rates of denture stomatitis and re-colonization of Candida which have been reported from 14 days up to a few months after cessation of the antifungal treatment. Nonetheless, it should be noted that the methods of disinfection can also have minor side effects such as staining and alterations of taste, and could lead to relapse of denture stomatitis after their use.

The results of this study should be interpreted with caution. First of all, the number of randomized controlled trials included in the meta-analysis was limited, and individual studies had small sample sizes. Furthermore, the methods in some studies were flawed, which could threaten their internal validity and introduce a risk of bias. This meta-analysis also demonstrated some statistical heterogeneity that can be explained by a lack of standardization and inconsistency in regards to Candida detection methods and microbiological analyses. The sources of heterogeneity could be considered as a hypothesis for further studies.

Thus, although randomized controlled trials are the accepted gold standard in the assessment of the effectiveness of interventions, they are not impervious to bias. It is suggested that conclusions should not be drawn when there are only small numbers of trials available with many clinical differences. Therefore, we should be cautious about making definitive conclusions and producing clinical practice guidelines based on these results. However, despite those limitations, the findings of this study can be used for treatment decision-making when integrated with the judgement of the clinician of the patient’s individual situation.

There is a need for properly designed randomized controlled clinical trials using standardized classifications and instruments of measure, in order to permit definitive meta-analytic results for the development of clinical practice guidelines to treat denture stomatitis.

This study also found a lack of randomized clinical trial comparing treatment approaches based on reducing the oral biofilm versus those that are based on reducing trauma. Such studies could shed light on the aetiology of denture stomatitis since randomized clinical trials provide the strongest evidence for both the effectiveness of a treatment and the causal effects of an underlying mechanistic pathway. However, longitudinal studies remain the best approach for etiologic research and to identify long-term benefits and harms of treatment modalities.

5. Conclusion

The findings of this review and meta-analysis suggest that disinfection methods could be considered as an adjunct or alternative to antifungal medications in the treatment of denture stomatitis.

Conflict of interest

The authors declare no conflict of interest with respect to authorship and/or publication of this article.

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