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Evidence Regarding the Treatment of Denture Stomatitis

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Abstract

Denture stomatitis is a common inflammatory condition affecting the mucosa underlying complete dentures. It is associated with denture microbial biofilm, poor denture hygiene, poor denture quality, and nocturnal denture use. Numerous treatment methodologies have been used to treat stomatitis; however, a gold standard treatment has not been identified. The aim of this systematic review is to report on the current knowledge available in studies representing a range of evidence on the treatment of denture stomatitis.

Denture stomatitis (DS) is the inflammation of the mucosa underlying a complete denture. This inflammatory condition is common, with a reported prevalence of 15% to 70% of denture wearers.[1] It is attributed to several etiologies including poor denture hygiene, poor denture quality, and nocturnal denture use. DS is an inflammatory mucosal disorder associated with a microbial pathogenesis.[2] Fungal infection is implicated by repeated isolation of opportunistic microbes from dentures of DS patients. Specifically, *C. albicans* is frequently implicated in DS.[3] Additionally, *C. glabrata, C. tropicalis*, and other fungi from the *Candida* species have been isolated from DS patients and their dentures.[4] Typically, more than one yeast species can be isolated intraorally.[5]

A prominent etiologic factor for DS is the measured level of *Candida* in the denture and saliva. Other factors, such as denture quality, xerostomia, and the presence of *Candida* in the mucosa, are of lesser importance.[7] The covariables identified in studies of DS and *Candida* infection include poor denture hygiene, poor denture quality, nocturnal denture use, impaired salivary flow, and compromised immunity; however, disagreement remains regarding the significance of these risk factors.[6,7] Understanding the relative roles of these potential risk factors is an important prerequisite for directing the proper management and treatment of this condition.

DS is characterized by several classical signs but few symptoms. It is rarely associated with severe pain or discomfort. It is often associated with angular chelitis.[8] The spectrum of DS is captured by the Newton classification system. This system stratifies the disease as localized inflammation or pinpoint hyperemia (type 1), diffuse erythema associated with the denture-contacting mucosa (type 2), and papillary (granular) hyperplasia of the keratinized mucosa (type 3).[9] The progression of DS without treatment may lead to systemic infection. In immunocompromised patients, the fungal component of DS can be devastating. Individuals with uncontrolled diabetes, HIV, and nutritional deficits, and organ transplant patients can develop deep tissue infections that can be very difficult to manage.[10] Relapse is common among immunocompromised patients after cessation of fungal agents.[11]

DS is a chronic condition that challenges treatment. Treatments involve local and systemic antifungal therapies, reduction or eradication of denture-related biofilm, laser treatment of the affected mucosa, or combination approaches. This diversity in treatment approaches is evidenced in a recent meta-analysis of

the treatment of DS that included 14 studies comparing different modalities of treatment.[13] The authors concluded that there was no difference between various disinfection methods and antifungal treatment when evaluated at the clinical or microbiological level. Given the breadth of experience reported in management of DS, the diversity of methods and therapeutic targets, a broader assessment of DS treatments is warranted. The aim of this systematic review is to summarize knowledge presented using a range of evidence (beyond randomized clinical trials) on the treatment of denture stomatitis.

Materials and methods

The intent of this review is to aid clinicians in establishing guidelines for the treatment of denture stomatitis. As such, a broad search was conducted, and inclusion criteria were established. These include the following:

1. Human clinical study, or samples taken from human subjects
2. Clinical trials, case series, observational studies (cross-sectional, longitudinal studies), and case control studies that tested/reported interventions to treat denture stomatitis
3. Inclusion of at least ten subjects
4. Investigation to include complete denture prostheses without the use of dental implants in one or both arches
5. Publication not more than 20 years old
6. Publication in peer-reviewed journal
7. Manuscript in English

An electronic search of publications to August 10, 2013 was established using five databases. The databases searched included PubMed, Embase, Google Scholar, ADA Evidence Based Database, and the Cochrane Collaboration Database.

The main search terms used in the databases were as follows: "denture stomatitis," "oral candidiasis," "oropharyngeal candidiasis." The combined search terms used in the database were as follows: "denture stomatitis" and "etiology," "*candida*" and "denture," "oral candidiasis" and "denture," "*candida albicans*" and "denture," "*candida*" and "edentulism," "*candida*" and "denture stomatitis," "denture stomatitis" and "treatment," and "denture stomatitis" and "prognosis."

A total of four reviewers completed the review by reading full-text articles and collecting relevant information in a data extraction table. Categories included in this table were as follows: primary authors, study design, the number of included subjects, and the follow-up period. The remaining categories of the table included the treatment and outcome of treatment evaluated. One table was made for healthy subjects, and one was made for immunocompromised subjects. A comprehensive statistical meta-analysis was not performed.

Results

The electronic search identified 2360 articles. Title and abstracts were screened by two authors independently for possible inclusion in the review. Following this review, 1766 were excluded, as they did not meet inclusion criteria. A total of 594 articles judged to be relevant by the title and abstract were read by a team of reviewers. Following article review, an additional 387 were excluded, as they did not meet inclusion criteria or were duplicates. Of the final 207 articles, 67 were relevant to complete denture stomatitis treatment methodology, and these were included in this review.

The included papers represented different levels of evidence. Among them, 64 prospective studies and 3 retrospective studies were reviewed. Among the prospective studies, 22 were cohort studies and 7 were cross-sectional studies. There were 33 randomized control trials (RCTs).

The included studies reflected outcomes of 5255 subjects. Patients were followed for a period of 1 day to 1 year. Among the studies, many did not differentiate between treatments for the maxillary versus the mandibular arch; however, most studies focused on the maxillary arch.

The included studies are summarized in Table 1 (for healthy patients) and Table 2 (for immunocompromised patients). A total of 62 articles evaluated healthy patients. A total of five articles evaluated immunocompromised patients. The studies range from prospective and retrospective cohort investigations, to cross-sectional observations to RCTs. The diagnostic criteria for oral candidiasis were not standardized among the studies.

The populations studied and the data collection methods are exceptionally varied. Treatments evaluated were grouped into eight main treatment categories. These include:

1. Antifungal therapy, including both systemic and topical application
2. Disinfectants and cleansers
3. Laser treatment of palatal tissue
4. Oral hygiene instructions
5. Fabrication of a new denture
6. Hard reline
7. Placement of a resilient liner or a tissue conditioner
8. Microwave disinfection

The treatments evaluated in healthy patients are summarized in Table 3. Thirty-six papers evaluated the effect of antifungal agents applied both locally and systemically. Of those, 34 papers revealed that treatment with an antifungal agent reduced DS in healthy patients. Two papers[15,35] showed no difference in outcome (Table 1). One article[37] compared single-agent antifungals to combination therapy. The results revealed that combination therapy of antifungal agents showed an increased benefit compared to single agent antifungals (Table 1).

Sixteen papers evaluated the use of disinfectants and/or denture cleansers in DS treatment. Thirteen of 16 papers reported that treatment improved the condition (e.g., Table 1[6,21]). Interestingly, nine papers included the use of alternative medicines (extracts, pollens) for the treatment of DS (Table 1[5,8,13-15,31,45,52]). Among these, the majority of studies demonstrated reduction of DS and equivalence with comparisons to antifungal agents. No negative control (sham treatment or simple cleansing) was included in these studies. Two papers[39,62] demonstrated that hard reline material placement successfully reduced DS (Table 1). Denture disinfection was also examined. Five articles evaluating microwave disinfection resulted in a positive outcome (Table 1[44,49]). Fabrication of a new complete denture was shown to be effective

Table 1 Included studies evaluating the treatment of complete denture stomatitis in healthy patients

Authors, year	Prospective, retrospective	Number of subjects (N total)	Follow-up period	Treatment evaluated	Treatment outcome
Abaci, 2011[18]	Prospective	110		Amphotericin B, Fluconazole, 5-fluorocytosine, caspofungin terbinafine	Sensitivity of *C. albicans* to amphotericin B (61%), fluconazole (44%), 5-fluorocytosine (100%). *C. glabrata* (second most isolated species) susceptibility to caspofungin terbinafine (100%) and 5-fluorocytosine (100%). Caspofungin terbinafine and 5-fluorocytosine are suggested to be used in the treatment of fungal infections
Amanlou et al, 2006[19]	Prospective	24	0, 7, 14, 21, and 28 days	Miconazole 2% gel versus Zatana multiflora 0.1%	Miconazole reduced colony count more than Zatana multiflora. Zatana multiflora reduced erythema more than miconazole.
Andrucioli et al, 2004[20]	Prospective	24	60 days	Mechanical method with experimental denture paste and soft-bristle toothbrush for biofilm removal	Experimental product was efficient in the removal of denture plaque biofilm.
Arikan et al, 1995[21]	Prospective	60	14 days	Fluconazole, fluconazole plus, chlorhexadine, new fitting denture	For generalized simple DS fluconazole in conjunction with chlorhexidine resulted in greater improvement of palatal inflammation. Localized simple stomatitis patients improved with new fitting dentures.
Bakhshi et al, 2012[22]	Prospective	40	4 weeks	Compared nystatin to garlic extract	The changes in the length and width of erythema at different times (4-week treatment) according to the type of treatment were found to be significant, while an accelerated recovery was demonstrated for nystatin ($p < 0.001$). Both regimens resulted in significant recovery ($p < 0.0001$). Greater satisfaction with the use of garlic rather than nystatin was mentioned ($p < 0.0001$). Nystatin was more effective at earlier time points.
Banting et al, 1995[23]	Prospective	23	3 months	The effectiveness of an antifungal soaking solution (nystatin) as an adjunct to a nystatin lozenge compared to soaking dentures in tap water and using lozenges.	Compared to tap water, use of antifungal denture soaking solution showed no detectable difference in presence of *C. albicans* over a 3-month period, but the signs and symptoms of oral candidiasis resolved in all subjects after therapy. Nystatin denture soaking solution was not shown to provide any added benefit compared to nystatin lozenges alone.
Banting and Hill, 2001[24]	Prospective	34		(1) Scrub and microwave max denture for 1 minute at 850 W versus (2) soak denture in chlorhexidine overnight. All subjects received the same course of topical antifungal medication (nystatin 300,000 IU lozenges 3× daily for 14 days	After 3 months, one (8%) patient in the microwave group and 12 (63%) patients in the denture soak group demonstrated pseudohyphae on the cytological smears.
Barnabe et al, 2004[25]	Prospective	28	15 days	Coconut soap versus coconut soap with 0.05% sodium hyperchlorate	$p < 0.05$ confidence level is (1) significantly reduced DS signs, (2) *C. albicans* count not reduced, (3) *S. mutans* reduced, (4) controlled biofilm.
Beyari, 2011[14]	Prospective	40	6 months	Three types of denture cleansers versus control (no cleanser)	Chemical cleansing of dentures decreased the total number of CFU of microorganisms and the number *S. mutans*. Condition of mucosa also improved with the decrease in microorganisms.
Blomgren et al, 1998[27]	Retrospective	60		Oral fluconazole and nystatin	No significant difference between the two groups treated with fluconazole and nystatin. Fluconazole showed considerable improvement in 87% of patients, nystatin showed improvement in 80% of patients. Fluconazole was reportedly easier to take. For immunocompromised patients, systematic treatment is recommended. Local antifungal is recommended in case of local predisposing factors (hyposalivation, local steroids, etc.).

(Continued)

Table 1 Continued

Authors, year	Prospective, retrospective	Number of subjects (N total)	Follow-up period	Treatment evaluated	Treatment outcome
Brosky et al, 2003[28]	Prospective	20		Molloplast B and MPDS-SL—experimental (resilient denture liners)	Candida growth on Molloplast B was not significantly different from growth on MPDS-SL. The rates of culture-positive testing (65% on Molloplast B samples and 45% on MPDS-SL samples) did not differ between the two resilient denture liners. Most common species were *C. albicans* and *C. glabrata*.
Budtz-Jorgensen et al, 2000[15]	Prospective	272		Preventative oral health program	Preventative program was effective in reducing the colonization of the oral mucosa and dentures by *Candida*. Reduction of number of patients with positive cultures.
Campelo et al, 2002[29]	Prospective	75		Essential oil Cymbopogom citratus (cream and spray), nystatin	CCR-2000 cream and spray are as effective as nystatin in reducing oral *Candida*. CCR-2000 cream and spray could be recommended to reduce oral yeasts, to prevent oral lesions related to *Candida*.
Capistrano et al, 2013[30]	Prospective	45	4 weeks	(1) 2% concentration miconazole gel, (2) 2.5% concentration propolis gel, (3) 24% concentration propolis mouthwash (propolis—a resinour MH collected by bees from various plants)	No difference among groups; all had a significant reduction or a complete remission of DS and a significant reduction of *C. albicans* colonies.
Catalan et al, 2008[31]	Prospective	27	12 days	Melalevca alternifolia oil + CoeComfort treatment, Nystatin + Coe Comfort, and Coe Comfort	No difference
Cross et al, 2000[33]	Prospective	40	6 months	Cyclodextrin solution of itraconazole (compared) itraconazole capsules 100 mg twice daily for 15 days	Liquid and capsule preparations of itraconazole are equally effective adjuncts in the treatment of DS. The side effect profile reveals that itraconazole capsules are the preferred formulation.
Cross et al, 1998[32]	Prospective	20		Fluconazole capsules (50 mg daily for 14 days)/itraconazole capsules (100 mg a day for 15 days)	Fluconazole and itraconazole were of comparable efficacy in the treatment of DS, on the basis of reduction in palatal erythema and mycological culture. Mycological cure was rare.
Cross et al, 2004[17]	Prospective	22	3 years	(1) capsular form of itraconazole (100 mg 2× a day) versus (2) 100 mg of itraconazole in the form of a mouthwash (10 mL 2× a day), swished and swallowed	A complete and consistent change of yeast species from baseline was observed in six patients after 6 months and at 3 years. The remaining five patients were yeast-free at the follow-up assessments. The recurrence of DS in patients who maintained a high standard of denture cleanliness was low. Although itraconazole was beneficial in reducing the fungal load, there may be strain persistence or subsequent recolonization of the oral cavity by a broader range of potentially less sensitive yeast species.
Czerninski et al, 2010[34]	Retrospective	14		Clotrimazole varnish (sustained release) compared to commercial varnish	Developed sustained (slow) release varnish can be applied in patients at lower frequency. Novel Clotrimazole sustained-release varnish can serve as the basis of a new treatment approach for Candidiasis.
Dar-Odeh and Shehabi, 2003[35]	Prospective	167		Amphoterecin B, Fluconazole	100% of Candida isolates were susceptible to amphotericin B, and only 25 (75%) were susceptible to fluconazole.

(Continued)

Table 1 Continued

Authors, year	Prospective, retrospective	Number of subjects (N total)	Follow-up period	Treatment evaluated	Treatment outcome
de Andrade et al, 2011[36]	Prospective	77	Baseline and 21 days	(1) Effervescent tablets, (2) ultrasound device, (3) effervescent tablets and ultrasound, (4) water on species of *Candida* and *S. mutans.*	Effervescent tablets decreased *S. mutans* count. Candida did not show a difference among the methods examined.
de Andrade et al, 2012[37]	Prospective	60	21 days	(1) Brushing and soak in water overnight, (2) brush with water and 12% chlorhexidine soak nightly, (3) brush with water and 2% chlorhexidine soak nightly at 21 days	Soaking nightly in 12% chlorhexidine and 2% chlorhexidine both had the same effect on biofilm detection at 21 days. The effect was greater than brushing with water and soaking in water alone.
de Resende et al, 2006[38]	Prospective	136		Fluconazole and 5-flucytosine, amphotericin B, and itraconazole	Fluconazole and 5-flucytosine showed increased efficacy over amphotericin B and Itraconazole.
De Souza et al, 2009[39]	Prospective	11	21 days	(1) Oral and denture hygiene instructions and (2) instructions associated with the home use of a disclosing agent (1% neutral red)	Counts were low for all the tested species, and no significant difference was found between the tested interventions (Wilcoxon test, p values ranged from 0.157 to 1.000). The home use of a disclosing agent does not remarkably change the composition of denture biofilm.
Duyck et al, 2013[40]	Prospective	51	7 and 14 days	(1) H_2O storage, (2) dry storage, (3) H_2O and alkaline peroxide-based cleansing tablet storage	Water + alkaline peroxide-based cleansing tablet storage resulted in lowest bacterial level and lowest *C. albicans* level.
Egusa et al, 2000[41]	Prospective	12		PAFE (postantifungal effects) and CSH (cell surface hydrophobicity) to amphotericin and nystatin	PAFE nystatin = 5.99 (± 0.49H) → decrease in CSH 17.32%, and 83% of isolates. PAFE Amphotericin B = 8.73 (±0.93) → decrease in CSH 14.26% and 66% of isolates.
Frenkel et al, 2001[16]	Prospective	412	Baseline, 1, 6 months	Oral health care education	DS reduced significantly over 6 months compared to the control group ($p < 0.0001$).
Geerts et al, 2008[12]	Prospective	40	14 days	(1) Tissue conditioner, (2) tissue conditioner and 500,000 nystatin	(1) Yeast goes down to day 4 then up higher than pretreatment level. (2) Decreased up to day 7, increased, but lower than pretreatment.
Glass et al, 2011[43]	Prospective	51		Denture cleanser: Polident at room temperature, Polident and microwave	Most effective methods for sanitization of contaminated dentures; Polident cleanser at 65°C for 5 minutes or soaking the dentures in US or European Polident for 8 hours daily.
Grimoud et al, 2005[44]	Prospective	110	3 months	Oral hygiene protocol implemented and evaluated at 3 months	A reduction was observed in the number of patients showing the highest degree of *C. albicans* and *C. glabrata* colonization (>50 CFU) from 41.9% at T1 to 24.9% at T2 ($p < 0.05$), and from 56.4% at T1 to 13.0% at T2 ($p < 0.05$), respectively. The number of patients with candidiasis fell significantly from 43.2% at T1 to 10.2% at T2. The OH protocol led to an overall decrease in *Candida* spp. colonization, a significant reduction in the number of candidiasis.
Herrera et al, 2010[45]	Prospective	21		Six commercial propolis extracts	Propolis extracts are capable of inhibiting the development of *Candida* spp.
Jose et al, 2010[47]	Prospective	16		Four types of denture cleansers were evaluated	Denture cleansers tested exhibit effective anti-*C. albicans* biofilm activity both in terms of removal and disinfection. Residual biofilm retention was observed then can lead to regrowth and denture colonization. Still need mechanical disruptive methods. All cleansers reduced the metabolic activity by more than 80% following overnight immersion.

(Continued)

Table 1 Continued

Authors, year	Prospective, retrospective	Number of subjects (N total)	Follow-up period	Treatment evaluated	Treatment outcome
Kadir et al, 2007[48]	Prospective	55		Chlorhexidine gluconate (brief exposure of 30 min). Two subtherapeutic concentrations: 0.002% to 0.012%	Exposure of isolates to chlorhexidine reduced the phospholipase production significantly. No significant difference in the number of *C. albicans* isolates (isolates producing phospholipase). Subtherapeutic levels of chlorhexidine gluconate can modulate *Candida* phospholipase activity, thus suppressing the pathogenecity of *C. albicans*.
Kisnisci et al, 1997[49]	Prospective	21		(1) Systemic antifungal therapy with fluconazole (14 days, 1 tablet of 50 mg a day), (2) topical nystatin mouthwashes (14 days, 4 times a day), (3) control	Systemic and topical antifungal therapies are both effective. Somewhat high success rates were obtained by only cleaning dentures. Topical treatment with nystatin is found more effective than fluconazole. The first choice for treatment would be topical therapy and cleaning of denture. Systematic therapy may be suggested as an alternative.
Koga-Ito et al, 2006[50]	Retrospective	60		Fluconazole, itraconazole, amphotericin B, flucytosine	Resistance to antifungal was not observed in isolates.
Koray M et al, 2005[51]	Prospective	61		Influence of Fluconazole capsules and of Hexetidine mouth rinses	*C. albicans* counts in saliva, lesions, and denture were significantly lower after treatment with all three protocols. No significant difference between results from each group. Group 2, Hexitidine mouthrinse only showed similar results with the least complications.
Lamfon et al, 2005[52]	Prospective	10	72 hours	Antifungals: (1) Miconazole, (2) Fluconazole, (3) Chlorhexidine, (4) Combinations.	Single agent miconazole, fluconazole, or chlorhexidine resulted in no inhibitory effects. The combination therapy did result in inhibition.
Marei et al, 1997[54]	Prospective	18		Denture removal versus relined dentures with TC, versus application of laser irradiation for lesions while continuing to wear dentures	The results revealed that lesions in the group treated with laser irradiation were clinically superior in healing when compared with the other groups. Histologic evidence of the therapeutic effect of lasers in healing denture-induced mucosal lesions was demonstrated. Densitometric evaluation showed an increase in the optical density of alveolar bone underneath the irradiated lesions compared with untreated lesions. These findings suggest the effect of therapeutic laser treatment on both soft tissue and bone with subsequent improvement of denture foundation after treatment of denture-induced mucosal lesions.
Marin Zuluaga et al, 2011[55]	Prospective	44		Tissue conditioner (changed weekly) versus acrylic hard reline material	Tissue conditioner had significantly ($p < 0.001$) greater resolution time, but both treatments were effective.
Martin-Mazuelos et al, 1997[53]	Prospective	335	Initial visit, 14 days, 15 days, and 1 month	(1) Fluconazole administered, then (2) Itraconazole administered to fluconazole-resistant subjects	(1) Clinical 97%, microbial 78% cure after fluconazole. (2) Itraconazole. Clinically cured: 100%. Microbially cured: 77%
Maver-Biscanin et al, 2004[56]	Prospective	70	5 days	(1) Irradiation 685-nm laser for 10 minutes (30 mW), (2) irradiation with 830-nm laser for 5 minutes (60 mW), (3) placebo (sham irradiation), (4) antimycotic antifungal oral gel	Had a fungicidal effect: Irradiation 685-nm laser for 10 minutes (30 mW) and irradiation with 830-nm laser for 5 minutes (60 mW). Placebo had no effect.
Mima et al, 2012[57]	Prospective	40	0, 15, 30, 60, and 90 days	(1) Nystatin (100,000 IU) 4× daily for 15 days (clinical success rate 53%), (2) photodynamic therapy (PDT) 455 nm 3× daily for 15 days (clinical success rate 45%)	Both treatments reduced CFU/mL at end of treatment ($p < 0.05$). Photodynamic therapy was found to be as effective as topical treatment.

(Continued)

Table 1 Continued

Authors, year	Prospective, retrospective	Number of subjects (N total)	Follow-up period	Treatment evaluated	Treatment outcome
Mohammad et al, 2004[58]	Prospective	30		Dioxident 2× daily for 1 minute and soak overnight ClO_2 for 10 days	ClO_2 significantly improved clinical experience and microbial count ($p < 0.001$) after treatment.
Neppelenbroek et al, 2008[59]	Prospective	60	30 days	(1) Control, (2) microwave 650 W, 6 minutes 2× a day for 30 days, (3) microwave 650 W, 6 minutes 2× a day for 30 days + Miconazole 3× a day for 30 days, (4) Miconazole three times a day for 30 days	Microwave (650 W) and microwave + miconazole were effective. Microwaving dentures dramatically reduced *Candida* recurrence at follow-up.
Pinelli et al, 2013[62]	Prospective	30	30 days (two examinations, one at 15 days and one at 30 days)	*Ricinus communis* versus nystatin and miconazole	For MIC, *R. communis* significant differences showing clinical improvement were observed between the 15th and 30th days. No differences were seen in the nystatin group. *R. communis* is an effective treatment for reducing the clinical signs of DS. *R. communis* effectiveness was similar to that of miconazole and can be considered a viable treatment to conventional treatments in institutionalized elderly.
Pinto et al, 2008[63]	Prospective	140		Fluconazole	All *C. albicans* strains showed sensitivity to fluconazole.
Pinto et al, 2008[64]	Prospective	55	45 days, then 64 days and after	Nighttime immersion 10% vinegar overnight for 45 days	Significant decrease in *C. albicans* and significant decrease in DS 70.8% to 47.9%.
Ribeiro et al, 2012[66]	Prospective	60		PDT procedures (P505, P1005, P50G, and P100G)	No microbial growth after PDT was observed in 60%, 53%, 47%, and 40% of dentures (no colony growth on all culture media after PDT). PDT was effective in disinfecting dentures (four treatments disinfected 90% of microorganisms on the dentures)
Ribeiro et al, 2009[65]	Prospective	30		Two exposure times of microwave irradiation (2 minutes and 3 minutes at 650 W)	Microwave irradiation for 3 minutes resulted in sterilization of dentures. 2-minute significant decrease in *Candida spp*. Microwave irradiation for 3 minutes may be a potential treatment to prevent cross contamination.
Salonen et al, 1996[67]	Prospective	49		(1) Miconazole 2% gel 3× to 4× daily on denture for 4 weeks, (2) Fluconazole 50 mg 1× a day for 2 weeks, (3) control group received new dentures. (Patients instructed not to wear dentures at night during study and for 6 months afterward)	(1) Group treated with miconazole showed healing in 58% of subjects. (2) Group treated with fluconazole showed healing in 77% of subjects. Overall 64% of patients receiving antifungal therapy showed healing. Control group showed positive healing in 20% of subjects. Method of medication (local or systemic) did not contribute significantly to the healing.
Sanita et al, 2012[68]	Prospective	40	90 days	Microwave denture disinfection versus nystatin treatment	40% of treated patients were cured by the end of treatment. There was no statistically significant difference in microbiologic and clinical outcomes between the two groups. Both treatments were considered successful in reducing the clinical signs of DS and significantly reducing the values of CFU's/MI from the palates and dentures.
Santos et al, 2008[69]	Prospective	33	Baseline and 1 week	Propolis versus miconazole gel (Daktarin)	Both Propolis gel and miconazole gave complete clinical remission.
Sefidgar et al, 2010[70]	Prospective	30		Artemisia Sieberi mouthwash (1%) versus nystatin mouthwash	No statistically significant difference in healing time between the 2 groups. Outcomes of treatments between groups were the same. Artemisia mouthwash (1%) could be as effective as nystatin in treatment of DS.

(Continued)

Table 1 Continued

Authors, year	Prospective, retrospective	Number of subjects (N total)	Follow-up period	Treatment evaluated	Treatment outcome
Sholapurkar et al, 2009[71]	Prospective	89	2 weeks	Fluconazole mouth rinse, clotrimazole mouth paste	Mycological eradication, 88.8%. Clotrimazole mouth paste 85.71%.
Silva et al, 2012[72]	Prospective	60		(1) Nystatin oral rinse, (2) Microwave disinfection, 3× daily for 14 days	Both nystatin oral rinse and microwave disinfection reduced clinical signs of DS. Species isolated in subsequent appointments were reduced in frequency from 98% to 53%, *C. glabrata* frequency reduced from 22% to 12% and *C. tropicalis* frequency was reduced from 25% to 7%.
Taillandier et al, 2000[73]	Prospective	305	2 weeks	Fluconazole oral suspension versus Amphotericin B oral suspension	122 (81%) fluconazole-treated and 135 (87%) amphotericin B-treated patients were clinically cured or improved. Mycological cure rates were 35% and 46% for fluconazole and amphotericin B, respectively. The symptoms of burning sensation and buccal pain resolved significantly sooner ($p < 0.05$) in fluconazole-treated patients.
Uludamar et al, 2010[75]	Prospective	90		3 brands of alkaline peroxide tablets (Polident, Efferdent, Fittydent) and 2 mouthwashes (CloSYS II and Corsodyl)	No statistically significant difference among Polident, Efferdent, and control group in any treatment period. Fittydent showed a significantly greater decrease in *Candida* after the 60-minute time. CloSYS II and Corsodyl had a significant decrease in the number of CFU compared to control group at all time periods.
Uludamar et al, 2011[75]	Prospective	60	15 days	(1) Tissue conditioner only, (2) Dioxident mouthrinse (0.8% chlorine dioxide medication) and denture soak in the solution overnight, (3) Corsodyl mouthrinse (0.2% Chlorhexidine gluconate) and denture soak in the solution	Group 1: 65% responded to treatment, 40% cured, 25% showed improvement. *C. Albicans* colony count decreased slightly. Group 2: 85% of group responded to treatment, 60% cured, 25% showed improvement. Group 3: 90% responded to treatment, 70% cured, 20% showed improvement. Groups 1 and 2: Statistically significant decrease at end of treatment of *C. albicans* colonies. The treatment of DS with tissue conditioner alone is not sufficient to control *Candida* pathogenicity. The use of a tissue conditioner for the treatment of DS had no effect on eradicating the hyphal form of *C. albicans* identified in smears, and its effect on eradicating yeast cells was insignificant, but it did contribute to decreased palatal inflammation. Mouthrinses of both Dioxident and Corsodyl are more effective in eliminating palatal inflammation, candidal colonization, and hyphae.
Vasconcelos et al, 2003[76]	Prospective	60		Punica granatum (pomegranate) gel versus miconazole gel. Treatment prescribed: use gel 3× a day for 15 days	*P. granatum* showed a similar response rate to Miconazole, and *Candida* colonization was reduced as well. A similar performance compared to miconazole gel was observed for the negativity of *Candida*. The clinical and laboratory results show improvement with the use of *P. granatum*. No side effects were noted.

(Continued)

Table 1 Continued

Authors, year	Prospective, retrospective	Number of subjects (N total)	Follow-up period	Treatment evaluated	Treatment outcome
Vigild et al, 1998[77]	Prospective	264	1 year	Professional dental care and education	There was a significant decrease in the presence of DS. An improvement in denture hygiene was also observed.
Webb et al, 2005[78]	Prospective	60	1 week	(1) Sodium hypochlorite soak, (2) microwaving, (3) control	Results: Both hypochlorite and microwave irradiation significantly reduced the numbers of *Candida* and aerobic bacteria on both dentures, and both methods significantly reduced *Candida* on the palate; however, palatal aerobic bacteria were not significantly reduced by either method, and the controls showed insignificant changes at all three sites for both *Candida* and aerobes.
Zuluaga et al, 2011[79]	Prospective	44	4 weeks	Tissue conditioner (TC) replaced weekly versus acrylic hard reline material (AHRM)	Both TC and AHRM were effective in the management of DS. Significant differences were found in the DS resolution time ($p < 0.001$), taking longer for the TC. As such, AHRM required fewer appointments for the patient.

(Table 1[4]). Seven papers evaluated the use of resilient liners or tissue conditioners to treat DS. Of the seven evaluated, four showed an improvement in DS when a liner or tissue conditioner was placed. One article[28] (Table 1) revealed an initial improvement, but an overall increase in DS when tissue conditioner was used. Two articles[11,15] showed no difference (Table 1). Targeting of the denture was a broadly successful, common therapeutic strategy, yet with reported limitations.[12]

Besides the direct treatment of the denture, laser treatment of tissues of DS patients was evaluated in three articles,[38,41,48] and all three revealed a decrease in DS (Table 2). In addition, control of biofilm through oral hygiene education and programming was discussed in five articles. Four showed an improvement in outcome, while one showed no difference (Table 2[24]). Of the 62 articles that evaluated healthy patients, a majority (42 studies) invoked some type of combined treatment strategy.

Far fewer studies have evaluated DS treatment in immunocompromised patients (Table 4). Four of these five papers evaluated the effect of antifungal agents applied both locally and systemically. Two[63,64] of the four studies involving antifungal agents showed a decrease in DS (Table 2), while two[66,67] showed no difference in DS (Table 2). No investigations examined the effects of disinfectants and cleansers on DS of immunocompromised patients. In addition, no studies evaluated the effect of a hard reline, laser treatment, microwave disinfection, new complete denture provision, or the use of tissue conditioners on the DS of immunocompromised individuals.

Discussion

This systematic review identified the spectrum of treatments used for DS and summarized the treatment outcomes. Recently, a systematic review with meta-analysis reported on the comparison of antifungal therapies versus alternative methods for treatment of DS. That review concluded that both disinfection and antiseptic methods were as effective as antifungal therapy in treatment of DS.[13] The present findings (Table 1) from a broader assessment of the literature are consistent with this recent meta-analysis. Further, when considering immunocompromised individuals with DS separately, antifungal therapy was consistently reported to reduce or eliminate DS (Table 2).

While the intent of this review was to include a broad set of reports in an effort to gain more information, several limitations are imposed by the nature of these studies. Foremost among them is that the diagnostic criteria (Newman Classification) for DS were not fully represented and employed among the studies. Comparisons and resulting conclusions suffer from clinical heterogeneity due to unknown inclusion based on severity. The standardization of diagnostic criteria among inclusion criteria for these studies may influence or improve assessments. Future studies are needed to define the influence of diagnostic classification (severity) on treatment outcomes.

Edentulism is a chronic condition influencing the individual for a lifetime. Yet, DS and its treatment were considered in terms of acute interventions by most of the included studies. This systematic review revealed few studies that evaluated therapy longer than 90 days. In a 6-month evaluation, the authors concluded that the use of denture cleansers reduced the number of microorganisms and diminished stomatitis.[14] In a 3-year follow-up study involving a small number of patients, Cross et al[17] stated that the recurrence of DS in patients who maintained a high standard of denture cleanliness was low. It is unknown if recurrent or repetitive infection and inflammation is prevalent among denture wearers.

Most studies included in this review represent small cohort studies or small prospective comparative trials. In an alternative epidemiological approach, Budtz-Jorgensen et al[4] evaluated the effectiveness of an oral health program on the prevalence of high

Table 2 Included studies evaluating the treatment of complete denture stomatitis in immunocompromised patients

Authors, year	Prospective or retrospective	Number of subjects (N total)	Follow-up period	Treatment evaluated	Treatment outcome
Blignaut et al, 2002[26]	Prospective	589		(1) Amphotericin B, (2) Nystatin, (3) 5-fluorocystosine, (4) Clotrimazole, (5) Miconazole, (6) Ketoconazole, (7) Itraconazole, (8) Fluconazole	100% susceptibility to fluconazole was observed. *Candida krusei* (the second most common isolate) only 2.6% of isolates were susceptible to fluconazole and itraconazole. Very little difference was observed between the antifungal profile of South African isolates compared to isolates from the United States, *Candida* and South America.
Finlay et al, 1996[42]	Prospective	73	20 weeks posttreatment	Amphotericin B, Fluconazole	Improvement seen in 72% of Amphotericin B patients and 92% of patients receiving fluconazole. Mycological cure at end of treatment: 31% amphotericin B and 46% fluconazole. Fluconazole is safe and well-tolerated antifungal agent. Antifungal prophylaxis useful for patients undergoing radiotherapy.
Hilton et al, 2004[46]	Prospective	35	6 months	Instructions by dentist on improving oral hygiene; minimize sugar intake, self-diagnosis of candidiasis	Candidiasis recurrence at 6 months: 78% among intervention and 88% among controls.
Nittayananta et al, 2008[60]	Prospective	75		Clotrimazole troche was prescribed until lesions eradicated; then, two groups: txt with 0.12% chlorhexidine or 0.9% normal saline	The time to recurrence of oral candidiasis between the chlorhexidine and the saline group was not statistically significant.
Nittayananta et al, 2013[61]	Prospective	38	2 weeks	Lawsone methyl ether mouthwash versus chlorhexidine mouthwash	Use of lawsone methyl ether mouthwash for 2 weeks neither led to antifungal drug resistance nor significant changes in genotype of oral *Candida*. Thus, lawsone methyl ether may be an alternative mouthwash in prophylaxis of oral candidiasis among those at risk for developing the disease.

risk, frail, or dependent adults. Of the 237 residents, 147 wore dentures. There were no significant differences in the numbers of mucosal yeast cultures for experimental and control groups or between individuals with slight, moderate, or severe stomatitis at baseline; however, 18 months following the institution of an oral health program, there was a highly significant reduction in the number of yeast colonies and a trend to reduced DS among the affected population (24% reduction in prevalence of moderate or severe stomatitis). This study underscores the importance of managing oral hygiene for the edentulous patient.

In a single-blind randomized study that invoked an oral education program in nursing homes, Frenkel et al[16] enrolled 412 individuals of whom 294 wore complete dentures. Oral hygiene education was associated with a significant reduction ($p < 0.001$) in denture plaque scores at all visits during the 6-month investigation. Specifically regarding denture-induced stomatitis, significant reductions were observed at 6 months for Newton class II and III individuals who received oral hygiene education. The authors concluded that the simple education program resulted in sustained improvement in denture hygiene and denture-induced stomatitis.

There is variability in the management of patients within studies. For example, Cross et al,[17] who evaluated the impact of itraconazole on *Candida* species counts, indicated that patients who removed their dentures for sleeping increased from baseline (25%) to 70% at the 6-month follow up. Managing this and

Table 3 Treatment evaluated by strategies (healthy patients)

Treatment categories	Number of papers in this category	Number of papers with a positive outcome *(decrease in denture stomatitis)*	Number of papers with a negative outcome *(increase in denture stomatitis)*	Number of papers showing no difference in outcome	Paper (listed by reference number)
Antifungal (pharmacotherapy): includes both local and systemic	36	34	0	2	1, 2, 4*, 5, 10**, 13, 14, 15*, 16, 17, 18, 20, 23, 26, 28*, 31, 33, 34, 35, 36, 37+, 40, 41*, 42, 45, 46, 50, 51*, 52, 53**, 54, 55*, 56, 57*, 58*, 59
Disinfectant/ cleansers	16	13	0	3	3, 6, 7*, 8, 9, 19, 21, 22, 25, 29*, 32, 43, 47, 57*, 58*, 61*
Hard reline	2	2	0	0	39*, 62*
Oral hygiene program	5	4	0	1	12, 24, 27, 30, 60
Laser treatment	3	3	0	0	38*, 41*, 48
Microwave disinfection	5	5	0	0	7*, 29*, 44, 49, 51*, 55*, 61*
New complete denture	1	1	0	0	4*
Resilient liners and/or tissue conditioners	7	4	1	2	11, 15*, 28*, 38*, 39*, 58*, 62*

*Paper combined treatment strategies (paper included in each treatment strategy group); **no difference between tested interventions; +Single-agent antifungal showed no effect. Combination therapy showed positive effect

Table 4 Treatment evaluated by strategies (immunocompromised patients)

Treatment categories	Number of papers in this category	Number of papers with a positive outcome *(decreased denture stomatitis)*	Number of papers with a negative outcome *(increased denture stomatitis)*	Number of papers showing no difference in outcome	Paper (listed by reference number)
Antifungal (pharmacotherapy): includes both local and systemic	4	2	0	2	63, 64, 66, 67
Disinfectant/ cleansers	0	0	0	0	n/a
Hard reline	0				
Oral hygiene program	1	1	0	0	65
Laser treatment	0	0	0	0	n/a
Microwave disinfection	0	0	0	0	n/a
New complete denture	0	0	0	0	n/a
Resilient denture liners and/or tissue conditioners	0	0	0	0	n/a

other variables (denture quality, denture hygiene, etc.) may be needed in further investigation. Among the management strategies represented by the included publications, many involved antifungal agents applied to the tissues locally or systemically. In a recent investigation by Altarwaneh et al,[7] measurement of denture, mucosal, and salivary fungal counts revealed that the denture may be the prevalent site of infection and that saliva may be a reservoir of biofilm-derived pathogens. The importance of treating the denture of the affected patient should be emphasized.

The treatment of DS in healthy versus immunocompromised individuals suggested an approach to intervention that favored pharmacological treatment of the patient rather than other methods that targeted the prosthesis. While studies of healthy edentulous individuals suggest that targeted treatment of the prosthesis by direct mechanical or indirect hygiene measures is effective,

the importance of managing immunocompromised individuals using a prosthesis-targeted approach with or without pharmacological antifungal agents requires investigation. The observations made regarding immunocompromised individuals with DS indicate that the host response to infection is a key feature of DS. The individual susceptibility to biofilm-mediated stomatitis remains largely unexplored among otherwise healthy individuals.

Conclusion

This review revealed many strategies for treatment of denture stomatitis patients. The investigated treatments did reduce DS. The scope of treatment is broad and included strategies that targeted biofilm formation on the prosthesis as well as targeted approaches focused on treatment of a fungal infection of tissues. Clinical strategies commonly involved multiple approaches with a combined goal of eliminating pathogenic microorganisms and preventing reestablishment of a pathogenic biofilm through preventive hygiene measures. The common limitation of these studies was the duration of study. The period of time necessary to develop a DS-evoking pathogenic biofilm remains to be determined.

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