

Candida-associated denture stomatitis . Aetiology and management: A review Part 3. Treatment of oral candidosis

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Abstract

Treatment of oral candidosis with topical antifungal agents such as nystatin and amphotericin B is effective initially. However, medication can produce side effects in some patients and when therapy is stopped the condition can recur. Alternative treatment involving the use of antiseptics and disinfecting agents has been shown to play an important role in the control of dental plaque. The use of sodium hypochlorite as an overnight denture soak has been shown to eliminate denture plaque and recent investigations have demonstrated that microwave irradiation of dentures at a specified setting and exposure time is bactericidal and candidacidal.

Key words: *Candida albicans*, antifungals, denture stomatitis, chlorhexidine, sodium hypochlorite, microwave irradiation.

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Introduction

There is clear evidence that the management of Candida-associated denture stomatitis is complex due to its multifactorial aetiology. Current treatment includes control of denture plaque, and, with patient compliance, removal of dentures at night in addition to the use of antifungals. In this review the following factors are considered: use of denture lining materials containing antifungals, antiseptic mouth rinses, denture soaks, removal of denture trauma and attention to denture hygiene.

Treatment of oral candidosis

Antifungals

A number of *in vivo* studies have been carried out to investigate the treatment of oral candidosis with antifungal agents. Epstein *et al.*¹ showed that treatment with Mycostatin§ as a mouthrinse four times daily for two weeks resulted in a significant reduction in the number of Candida organisms in saliva and a marked improvement in the disease; however, the condition recurred rapidly after cessation of treatment.

Epstein² emphasized the importance of topical antifungal agents for the prevention and treatment of oral candidosis. It was shown that amphotericin B and Mycostatin bind to ergosterol in the cell membrane of Candida organisms, causing changes in permeability, leakage of cell contents and cell death. It was noted that nystatin, although useful for topical therapy in oral and pharyngeal candidosis, is poorly absorbed when ingested and most of the drug passes unchanged through the gastrointestinal tract. Amphotericin B, which is an effective topical agent, is the drug of choice for intravenous treatment of progressive and potentially fatal candidal infections. Both amphotericin B and nystatin have an unpleasant taste thus affecting patient compliance, and oral use may sometimes lead to gastrointestinal side effects such as nausea, vomiting and diarrhoea. In the case of amphotericin B, renal, bone marrow, cardiovascular or neurological toxicity may result.

Epstein² also mentioned that flucytosine, a fluorinated pyrimidine, may be useful for the

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treatment of disseminated fungal infections; the drug affects protein synthesis and inhibits DNA synthesis of *Candida*.² Also, griseofulvin which is fungistatic, and affects cell wall synthesis, DNA synthesis and mitosis was useful in the treatment of mucocutaneous candidosis. The imidazole compounds such as clotrimazole, miconazole, econazole and ketoconazole, are broad-spectrum antifungal agents which affect permeability of *Candida* membrane by interfering with the synthesis of ergosterol; they also bind more strongly to *Candida* enzymes than to mammalian enzymes. Clotrimazole, although the most potent agent, is only used topically, because of gastrointestinal and neurological toxicity; econazole exists in topical form only; miconazole and ketoconazole can be used both topically and systemically.²

MacFarlane and Samaranyake³ have emphasized that treatment of denture stomatitis involves strict denture hygiene measures and the use of antifungal agents. In particular, patients should be discouraged from wearing their dentures at night and the dentures should be soaked overnight in an antiseptic solution; topical treatment with amphotericin B was also recommended.

A number of studies have been carried out to test the efficacy of denture lining materials (tissue conditioners/soft liners) containing antifungals in the treatment of denture stomatitis. Odds⁴ considered that denture liners alone usually have no effect on *Candida* species, though Gruber *et al.*⁵ had shown that silicone soft liners and tissue conditioners (trade names not supplied) with zinc undecylenate incorporated (1.5% and 1.0% m/m respectively) eliminated candidal growth. Douglas and Walker⁶ demonstrated the inhibitory effect of Tempo, and Coe-Comfort¶ (tissue conditioners) incorporating Nystan** and confirmed the results with an *in vivo* investigation. Thomas and Nutt⁷ showed that Visco-gel†† (tissue conditioner) combined with nystatin powder was successful in inhibiting the growth of *Candida albicans*, *Candida krusei* and *Candida tropicalis*. However, there was lack of inhibition by Visco-gel alone and a Visco-gel/amphotericin B combination. *In vitro* studies showed that a ketoconazole-Visco-gel combination used as a tissue conditioner effectively removed and killed *Candida* associated with dentures, the effect continuing over a long period.⁸ Another *in vitro* study investigated a sustained-release delivery system for the treatment of denture stomatitis by using four antifungal agents incorporated into a tissue conditioner Lynal.‡‡ The antifungal agents were chlorhexidine, clotrimazole,

fluconazole and nystatin at low, medium and high concentrations.⁹ All drugs were released from the tissue conditioner, with inhibition of candidal growth at each concentration, and nystatin showing the greatest antifungal activity. Inhibition by chlorhexidine and clotrimazole were dose-related and fluconazole samples required pre-incubation at 37°C for activation.

Merkel and Phelps¹⁰ showed that sub-lethal amounts of amphotericin B inhibited the attachment of *C. albicans* to cultured mammalian cells, and blastospores, which were in their exponential phase of growth or had formed germ tubes, were the most sensitive to the drug. Other investigators demonstrated that sub-inhibitory concentrations of amphotericin B, nystatin, miconazole nitrate and 5-fluorocytosine inhibited adhesion of *Candida* species to buccal epithelial cells (BEC).¹¹ In addition, the outer cell envelope was affected, germ tube formation was suppressed, and the loss of extracellular polymeric material (EP), known to mediate adhesion, was increased. Mehentee and Hay¹² showed that sub-inhibitory concentrations of amphotericin B, ketoconazole and itraconazole reduced the adhesion of *C. albicans* to gastric and jejunal mucosa. The effect of the antifungal agent depended on its concentration, susceptibility of the strain and the source of the mucosal surface.

An *in vitro* study was based on the frequently made observation by Davenport¹³ and Budtz-Jorgensen¹⁴ that in cases of denture stomatitis *C. albicans* colonies are recovered more frequently from the tissue fitting surface of the acrylic resin denture than from the corresponding palatal mucosa.¹⁵ Hence the need for total removal of the yeast from the dentures of patients with the disease and the prevention of recolonization of the denture by *C. albicans*. Spiechowicz *et al.*¹⁵ evaluated the antifungal effectiveness of Mycostatin,§§ Peridex,, and Poly-L-histidine¶¶ on the surface of acrylic resin discs which were pretreated with the respective antifungal agents for 8 h.¹⁵ It was found that pretreatment with Poly-L-histidine did not inhibit *C. albicans* adhesion and growth whereas chlorhexidine was completely effective in preventing candidal attachment and growth on acrylic resin. If pretreatment of acrylic resin with nystatin was followed by drying, then the protection was similar to that provided by chlorhexidine.

Antiseptics and disinfecting agents

An *in vivo* programme involving the use of Listerine*** antiseptic (ethanol 0.26 mL, benzoic

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**Bristol-Myers Squibb, ?????.

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§§Oral Suspension, USP Pharmafair, Inc.

., Procter and Gamble, Cincinnati, Ohio, USA.

¶¶ICN Biomedicals, Costa Mesa, CA, USA.

***Warner-Lambert Co., Morris Plains, NJ, USA.

acid 1.5 mg, thymol 0.63 mg, eucalytol 0.9 mg per mL) and Mycostatin as mouth rinses and denture soaks over a period of 28 days resulted in a significant reduction in palatal inflammation and candidal colonization of dentures and palatal mucosa, although denture plaque scores did not differ significantly.¹⁶ In another study a 0.2% chlorhexidine gluconate mouth rinse used three times daily significantly reduced plaque, but there was no significant effect on the number of *Candida* organisms.¹⁷

Schwartz *et al.*¹⁸ compared antiseptic (Listerine), Nystatin Oral Suspension USP (100,000 units/mL) and control (5% hydroalcoholic) mouth rinses three times per day for 30 per cent over a 28-day period. It was shown that neither the denture microbial count nor denture stomatitis was reduced by the mouth rinses used. The authors also suggested that the denture may be a reservoir of reinfection and recommended that treatment should include antimicrobial treatment of the denture and removal of the denture for a period of time every 24 h.¹⁸

Epstein² has described the use of Peridex containing chlorhexidine gluconate, in the treatment of oral candidosis. The drug is a broad spectrum mouthrinse which is adsorbed on the surfaces of microorganisms, increasing permeability of cell membranes and causing precipitation of cytoplasmic contents. It was found that chlorhexidine bound to salivary pellicles as well as hard tissues in the oral cavity, resulting in chlorhexidine titres in saliva for 12 hours or more after rinsing. Although effective in the treatment of oral candidosis, unpleasant side effects included staining of the tooth surfaces and a bitter taste.

Lal *et al.*¹⁹ investigated the use of chlorhexidine gluconate in the form of Peridex both as a mouthrinse and a denture soak in the treatment of denture stomatitis. The study was for a period of 24 days and Peridex oral rinse containing 0.12% chlorhexidine gluconate was used twice daily and dentures soaked overnight in Peridex solution. It was found that chlorhexidine completely eliminated *C. albicans* on the acrylic resin denture surface and significantly reduced palatal inflammation. However, several weeks after the Peridex treatment was terminated, *C. albicans* recolonized the denture surface and palatal inflammation recurred. This investigation is interesting in that it raises the question as to whether the denture reinfected the palate or whether localized yeast infection of the mucosal surface occurs independently of the presence of *C. albicans* on the denture surface. The authors concluded that palatal inflammation was in response to direct yeast invasion of the mucosa, and recurring infection of the palate by *C. albicans* on the denture surface, and therefore they suggested that treatment of denture stomatitis

should include antimicrobial topical application to both denture and mucosa.¹⁹

In another study, poor denture hygiene and ill-fitting dentures were considered to be the main predisposing factors in the aetiology of denture stomatitis, and it was suggested that management of denture stomatitis should be directed at reducing microbial growth and improving adaptation of the denture.²⁰ This study compared the effectiveness of Listerine antiseptic mouthrinses and denture soaks, with Coe Comfort maxillary soft denture reliners (tissue conditioners) in reducing denture stomatitis. Over a 28-day period, the patients were asked to use Listerine antiseptic solution (20 mL) as a mouthrinse three times per day and as a denture soak for one hour each evening. The maxillary dentures in the reline group were relined at seven-day intervals and for both groups there was no mechanical cleaning of the dentures during the trial period. The results showed that reduction in inflammation in both Listerine and reline treatment groups was significantly greater than in the control group and soft denture relines significantly improved denture retention and stability. However, denture plaque was not significantly reduced and it was concluded that in the absence of other mechanical denture hygiene measures, the antiseptic rinses and relines were equally effective in reducing denture stomatitis.²⁰

Barkvoll and Attramadal²¹ examined the effect of the combination of Mycostatin††† and chlorhexidine digluconate‡‡‡ on *C. albicans* *in vitro* and found that the combination of the drugs was not effective. In another study, sub-inhibitory concentrations of aqueous garlic extract were shown to have inhibitory effects *in vitro* on the adhesion of *Candida* species to human BECs and blastospores treated with the extract had reduced ability to form germ tubes.²²

Sodium hypochlorite

A number of studies have been carried out to demonstrate the antifungal properties of denture cleansing agents. Ghalichebaf *et al.*²³ found that those with a high pH and sodium hypochlorite content such as Mersene,§§§ pH 11.0, were the most effective in removing denture plaque. Basson *et al.*²⁴ and Rudd *et al.*²⁵ also demonstrated the sterilizing effect of sodium hypochlorite as a denture soak while alkaline hypochlorites have been shown to eliminate denture plaque effectively *in vitro* even after short term exposures.²⁶ The effect of hypochlorite is due to the presence of undissociated hypochlorous acid (HOCl),²⁷ where concentration is dependent on pH, and which oxidizes sulfhydryl groups (-SH) of amino acids and proteins to the disulphide form (S-S).^{28,29}

†††Novo Industries A/S, Copenhagen, Denmark.

‡‡‡ICILtd., Cheshire, England.

§§§Colgate-Palmolive Co., New York, NY, USA.

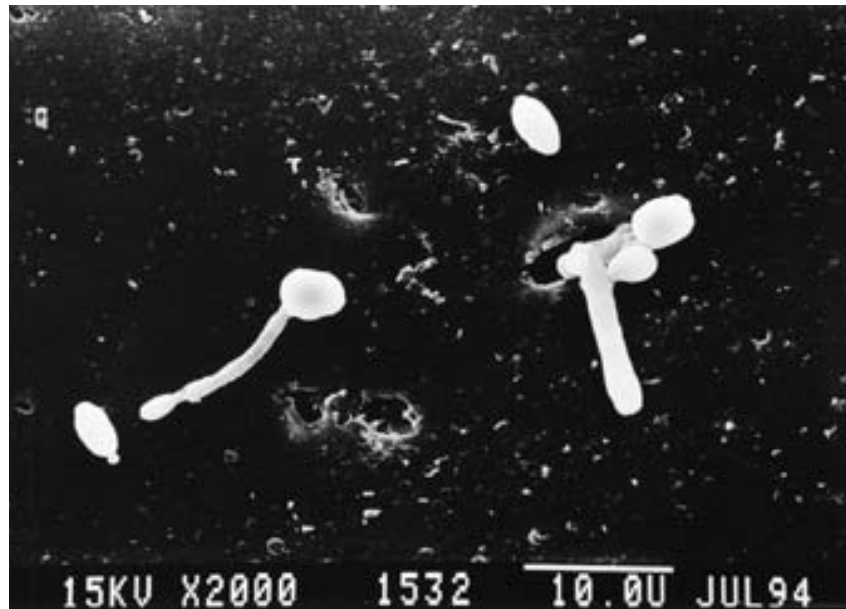


Fig. 1.—Scanning electron micrograph showing *Candida albicans* grown on denture acrylic for 48 h at 37°C, budding blastospores and hyphae penetrating the acrylic clearly visible (bar=10 µm).



Fig. 2.—Scanning electron micrograph showing damaged non-viable *Candida albicans* blastospore and hypha still adherent to acrylic resin after microwave treatment (bar=10 µm).

In another study it was shown that sodium hypochlorite in a concentration below the minimal inhibitory concentration reduced the adhesive abilities of *Candida* species and may therefore function as an effective antifungal agent when used as a denture soak in cases of denture stomatitis.³⁰ A report by Jagger and Harrison³¹ showed that a large number of people do not know how to clean their dentures satisfactorily and this could account for the deterioration of denture base material due to misuse of chemical cleansing agents.

It is clear from the above review of antimicrobial and antiseptic/disinfecting agents that there is currently no known totally effective treatment to prevent or reduce the incidence of denture stomatitis. One of the major factors that determines the success of a treatment regimen is patient compliance. Thus, an effective treatment regimen will combine the use of an antifungal agent with an easy-to-use application. This principle has been followed in a recent study which demonstrated that the soaking of acrylic dentures in 0.02% sodium hypochlorite overnight

for a period of several weeks effectively reduced the numbers of *Candida* and aerobic bacteria from the denture surfaces.³²

Microwave irradiation

To date there has been only one reported study of the use of microwave irradiation to sterilize microorganisms on denture surfaces.³³ Although other studies have been carried out to investigate the sterilization of microorganisms in association with dental instruments,³⁴ tissue culture vessels,³⁵ hydrophilic contact lenses,³⁶ medical instruments and apparatus³⁷⁻³⁹ and polyethylene catheters,⁴⁰ there is no other report relating to microwave sterilization of dentures. However, these studies provided ample evidence that microwave irradiation at high setting and at specified exposure times is bactericidal and candidacidal. Rohrer and Bulard³³ showed that microwaving at high setting for eight minutes would sterilize acrylic dentures contaminated with *C. albicans* suspension but if the dentures were contaminated with a mixture of *C. albicans* and aerobic bacteria, a longer period of ten minutes would be required for sterilization. The authors used a modified microwave oven with a three-dimensional rotating device to which the dentures were attached and found no dimensional change in the dentures they microwaved. Thomas and Webb⁴¹ demonstrated the effect of microwaving on the dimensional stability of acrylic resin dentures, using an unmodified domestic microwave oven. It was shown that microwaving of dentures at medium setting (350 W, 2450 MHz) for six minutes caused minimal change which was considered to be harmless in the long term. In another study, it was demonstrated that microwaving of dentures at medium setting (350 W, 2450 MHz) for six minutes will destroy *Candida* (Fig. 1, 2) and aerobic bacteria on the denture surfaces.³²

Conclusions

The preceding information has indicated that *Candida* species, although constituting only a minor proportion of the oral microbiota, possess certain characteristics that are associated with their pathogenicity in medically and immunocompromised hosts. Of the oral candidal infections *Candida*-associated denture stomatitis is the commonest and because of the multifactorial nature of the disease, management is complex. Recent research has investigated plaque control, removal of dentures at night, the use of antiseptic and antimicrobial agents, antifungals and microwave irradiation as factors to consider in the treatment of *Candida*-associated denture stomatitis.

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