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Effect of antifungal agents on indwelling voice prosthetic biofilms

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Rehabilitating the lost voice of laryngectomy patients by insertion of a silicone rubber voice prosthesis is now generally considered to be superior to any other form of substitute voice production. However, a drawback of these implants is the rapid colonization by a mixed biofilm of bacteria and yeasts, mainly *Candida* species, leading to failure and frequent exchange of the implant. A strategy frequently applied by otolaryngologists is oropharyngeal yeast decontamination by using antifungal agents, despite the fact that there is no compelling evidence that prescription of antifungal agents will prolong the lifetime of voice prostheses. Moreover, the prophylactic use of antifungal agents contributes to the development of resistant strains. Alternative approaches to prolonging the lifetime of silicone rubber voice prostheses may be found in modification of the silicone rubber surface of the implant, diet supplementation with active, probiotic bacteria, or salivary substitutes with synthetic antimicrobial peptides. Curr Opin Otolaryngol Head Neck Surg 2000, 8:165–168

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The inability to speak is the most disabling consequence of total laryngectomy. Different methods of rehabilitating the lost voice of laryngectomy patients have been developed. The insertion of a silicone rubber voice prosthesis in a surgically created tracheoesophageal shunt was a major step forward in the voice rehabilitation of laryngectomy patients and is now generally considered to be superior to any other form of substitute voice production, such as esophageal and electrolarynx speech.

Voice prostheses are not permanent implants but need to be replaced when patients complain about leakage through or around the prosthesis and increased airflow resistance. Continuous exposure to saliva, food, drinks, and the oral microflora contributes to the rapid colonization by a mixed biofilm of bacteria and yeasts, leading to failure and frequent exchange of the implant. Explanted voice prostheses show not only biofilm formation on the implants [1], as shown in Figure 1, but also ingrowth of yeasts, mainly *Candida* species, into the silicone rubber [2].

Candida albicans is frequently isolated from the human oral cavity, yet few carriers develop clinical signs of candidiasis. Oral candidiasis reflects the ability of the yeast to colonize different oral surfaces and the variety of factors that predispose the host to *Candida* colonization and subsequent infection. The host's immune competence ultimately determines whether clearance, colonization, or candidiasis occurs. In the case of laryngectomy patients, predisposing conditions for increased *Candida* colonization such as the underlying disease, surgical and extensive drug therapy, reduced saliva flow rate as a side effect of radiotherapy, prosthetic tooth replacement, and the presence of the prosthesis itself can be demonstrated.

Use of antifungal agents

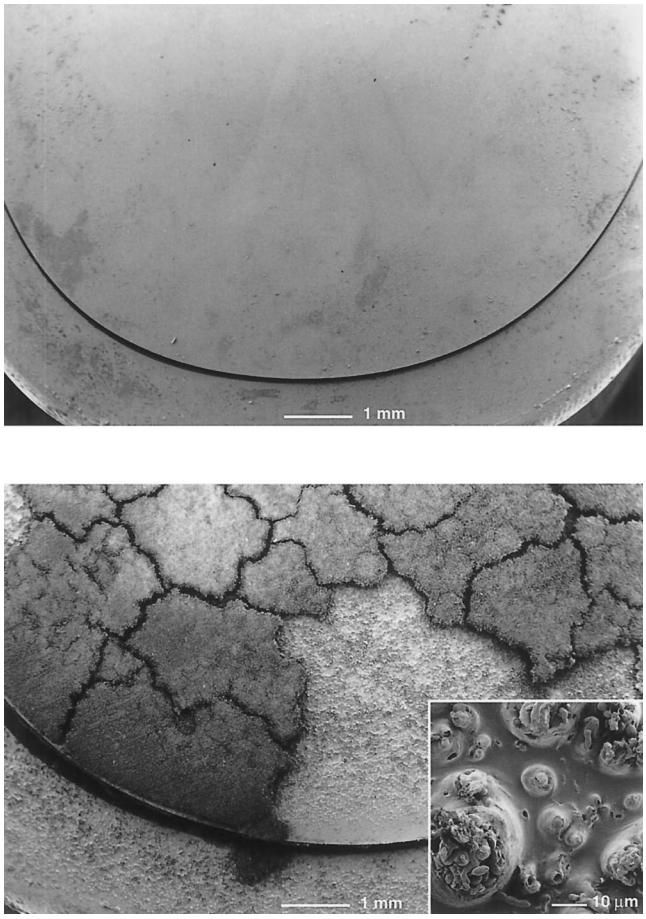
Oropharyngeal yeast decontamination by using amphotericin B lozenges and buccal bioadhesive slow-release tablets containing miconazole nitrate has been applied by ear, nose, and throat surgeons [3,4] to increase the lifetime of voice prostheses. These methods are especially in laryngectomy patients with prosthesis lifetimes of less than 2 months, although

scientific evidence regarding the efficacy of antimycotics in these applications is lacking.

Recently, Ackerstaff *et al.* [5] performed a nonrandomized, multi-institutional, controlled clinical trial on a novel anterograde replacement method comparing the lifetime of the second-generation indwelling Provox 2 voice prosthesis (Atos Medical AB, Hörby, Sweden) with that of the original Provox voice prosthesis. In the four clinics participating in this study, patients requiring replacement within 2 months due to valve failures caused by *Candida* overgrowth were advised to use anti-*Candida* medication on a daily basis, either by swallowing the liquid medication or by applying it directly into the prosthesis with a cleaning brush. Of the 157 patients included in the prosthesis lifetime analysis, 45 patients (28.7%) reported that they regularly used an anti-*Candida* drug (nystatin, amphotericin B, or fluconazole). In a proportional hazard regression analysis, it was subsequently demonstrated that the use of anti-*Candida* medication was not statistically significantly associated with the lifetime of the voice prostheses.

There is thus no compelling indication to prescribe antifungal agents for increasing the lifetime of voice prostheses in laryngectomy patients. Moreover, this prophylactic use of antifungal medication will contribute to the development of resistant yeast strains, whereas already the number of antifungal agents available is limited. However, these observations evoke the question, "Why is not there an association between biofilm formation, prosthesis lifetime, and the application of anti-*Candida* medication?"

Figure 1. Scanning electron micrographs of Groningen button silicone rubber voice prostheses, seen from esophageal side



Above, Unused Groningen button prosthesis. **Below**, Heavy biofilm formation on the valve side after use and ingrowth of biofilm organisms into the silicone rubber (inset).

Antimicrobial resistance of biofilms

Microbial biofilms are critical to the survival of the colonizing organisms in a wide variety of environments. The biofilm mode of growth protects microorganisms on voice prostheses against the host immune system and antibiotics or antimycotic agents [6]. These resistance properties of microbial biofilms have been attributed to an organization of the biofilm organisms within exopolymer matrices. Such exopolymers will chemically quench reactive biocides such as chlorine and peroxygens and bind highly charged antibiotics, thereby protecting the organisms of the inner layer of the biofilm against antimicrobial agents. Therefore, microbial biofilms are hardly treatable because of the difficulties of antimicrobials in penetrating this biofilm. Moreover, in case of biofilms on silicone rubber voice prostheses, the ingrowth of yeasts in the silicone rubber yields an extremely efficient shelter of the organisms against environmental attacks (Fig. 1). Recent work of Van Weissenbruch *et al.* [4] has shown that using antifungal agents in laryngectomy patients greatly decreases the prevalence of planktonic yeasts in saliva compared with those living in a biofilm in or on voice prostheses.

Alternatives for preventing biofilm formation on voice prostheses

Different strategies have been developed to prolong the lifetime of voice prostheses. Modification of the silicone rubber surface to discourage biofilm formation is an obvious strategy to prolong the lifetime of voice prostheses. Although voice prostheses will become covered by a conditioning film of adsorbed salivary components prior to the adhesion of bacteria or yeasts, experiments in the human oral cavity have demonstrated that the properties of this conditioning film are determined by the material itself [7]. By consequence, biofilm formation can be influenced by adjusting the properties of the voice prosthesis material or by surface modification.

Everaert *et al.* [8] demonstrated that biofilm formation on silicone rubber Groningen button voice pros-

theses over an evaluation period of approximately 2 to 8 weeks can be reduced by chemisorption of long perfluoro-alkylsiloxane polymer chains, owing to the high hydrophobicity and mobility of the chemisorbed polymer chains. However, the effect of this modification on the average lifetime of indwelling voice prostheses must still be determined. An invention has been patented [9] related to the discovery of a way to inhibit microbial growth on the surface of a medical device such as a voice prosthesis by forming the prosthesis of, or coating the surface with, a layer of a fluoropolymer. The patent claims an elongation of voice prosthesis lifetime by 133 days (or 28.1%) on average, but this claim is based on only three patients.

Within patient support groups in The Netherlands, laryngectomy patients have suggested that the consumption of buttermilk, containing antimycotic-releasing *Lactococcus lactis*, positively affects the lifetime of voice prostheses. This suggestion has been confirmed in an artificial throat model, in which the effects of daily buttermilk consumption on biofilm formation on silicone rubber voice prostheses have been simulated [10,11]. Similarly, Turkish yogurt containing *Streptococcus thermophilus* has been suggested to have such beneficial effects. Evaluations in the artificial throat model have furthermore indicated that the development of an oropharyngeal biofilm on silicone rubber voice prostheses can be delayed by exposure to suspensions of active probiotic bacteria, such as *L. lactis* 53 and *S. thermophilus* B [12••].

Many laryngectomy patients have salivary dysfunction as a result of surgical therapy, radiation therapy, aging, or medication. Low salivary secretion reduces the amounts of histatins in saliva, yielding better chances for opportunistic microorganisms such as *C. albicans*, because histatins are the most significant source of fungicidal activity in saliva [13]. Artificial salivary substitutes, commonly used by xerostomic patients and sometimes by laryngectomy patients, now mainly contain carboxymethylcellulose, animal mucins, or xanthan, but these substances present an excellent vehicle for novel antifungal agents [14]. Promising antifungal agents are synthetic salivary peptides, which can possess bactericidal and fungicidal activities [15••,16••]. Moreover, these salivary peptides so far have not been associated with the development of microbial resistance.

Conclusions

There is no compelling evidence that the prescription of antifungal agents will prolong the lifetime of voice prostheses in laryngectomy patients. The prophylactic use of antifungal agents in laryngectomy patients contributes to the development of resistant strains. Thus alternative approaches are called for. Such approaches to prolonging the lifetime of silicone rubber voice prostheses may be found in silicone rubber surface modification, diet supplementation with active, probiotic bacteria as can be found in certain dairy products, or salivary substitutes with synthetic antimicrobial peptides

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