The Laryngoscope

Evaluation of Prophylaxis Treatment of Candida in Alaryngeal Patients with Tracheoesophageal Voice Prostheses

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Objectives/Hypothesis: The objective of this study was to evaluate the effectiveness of nystatin and Biotène® mouthwash Oral Rinse for controlling *Candida* in total laryngectomy (TL) patients with a tracheosophageal voice prosthesis (TEP) because Biotène® mouthwash Oral Rinse is a less costly alternative to nystatin and requires less adherence time.

Study Design: Randomized, unblinded, crossover trial.

Methods: Twenty-one TL patients were randomized to receive nystatin followed by Biotène® mouthwash Oral Rinse, or the reverse order, after a basic oral-care phase (i.e., brushing teeth, cleaning dentures). A Provox® 2, 22.5 French TEP, which is an indwelling silicone voice prosthesis, was placed at the beginning of each phase. Patients were provided with oral care instructions at randomization and medication-specific instructions with each treatment's initiation. TEPs were processed and evaluated for *Candida* growth as colony-forming units (CFUs). Wilcoxon signed-rank tests were used for comparisons between treatments.

Results: Fifteen patients were available for comparisons of *Candida* counts (6 received nystatin; 9 received Biotène® mouthwash first). Overall, the median $\log_{10}$ (CFUs) remained high regardless of treatment (no medication: 8.9; nystatin: 8.7; Biotène® mouthwash: 8.4). However, the median counts for both nystatin and Biotène® mouthwash Oral Rinse were lower than those for no medication (difference [Δ]: −0.9 and −0.3, respectively), although only nystatin was significantly lower ($P = 0.02$). There was no significant difference between the two treatments ($P = 0.22$). Overall, median medication-adherence was high (97%), and Biotène® mouthwash adherence was significantly higher than that of nystatin (Δ: 7.6%; $P = 0.03$).

Conclusion: Nystatin and Biotène® mouthwash Oral Rinse had similar CFU levels, with nystatin showing a significant improvement over usual oral care. Biotène® mouthwash is a less costly alternative to nystatin, with a less complex treatment protocol that might make it preferable to patients and clinicians.

Key Words: Biotène® mouthwash, nystatin, laryngectomy, tracheoesophageal voice prosthesis, *Candida*.

Level of Evidence: 1.

***Laryngoscope*, 00:000–000, 2014**

INTRODUCTION

Since the development and use of the tracheoesophageal voice prosthesis (TEP) for voice rehabilitation, the colonization by *Candida* organisms on the TEP has been identified as a significant factor in its malfunction and a major reason for replacement.[1–3] Members of the *Candida* species are yeast-like organisms that are normal components of the oral flora in most individuals, as well as in the oropharynx and intestines. *Candida* may multiply and grow onto the silicone material of the TEP, which can lead to failure of the valve mechanism and subsequent aspiration of liquids into the airway or the degradation of tracheoesophageal voice. Prostheses are expensive and replacement is intrusive; thus, the prevention or delay of *Candida* infestation to improve overall TEP longevity is critical in patient care. Anti-*Candida* treatment has been shown to improve prosthetic life,[4,5] leading experts to advocate the use of oral chemoprophylaxis.[6] Traditionally, nystatin (an antifungal, polyene antibiotic) has been used as a prophylaxis against the growth of *Candida* on the TEP. However, this drug is expensive and patient compliance is often an issue due to its method of administration (5-minute swish twice daily).

Due to these factors, alternate therapies to treat *Candida* infestation may be beneficial. One potential candidate is topical oral rinse (Biotène® mouthwash Oral Rinse; GlaxoSmithKline, Brentford, United Kingdom), an artificial saliva containing three enzymes (lactoperoxidase, glucose oxidase, and lysozyme) specifically formulated to activate intraoral bacterial systems.[7] Biotène® mouthwash Oral Rinse is often recommended to TEP patients because the treatment for advanced-stage cancer of the larynx with total laryngectomy (TL), with or without radiation therapy, alters the physiological function of the aerodigestive tract, often resulting in xerostomia. As a

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Editor's Note: This Manuscript was accepted for publication October 21, 2014.

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This research was supported by the funding from the Milton J. Dance, Jr. Endowment, Inc. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

DOI: 10.1002/lary.25034

TABLE I.
Treatment Order by Study Arm With the Addition of Basic Oral Care at Each Phase.

	Phase 1	Phase 2	Phase 3
Arm 1	No medication	Nystatin	Biotène® mouthwash Oral Rinse
Arm 2	No medication	Biotène® mouthwash Oral Rinse	Nystatin

saliva substitute, Biotène® mouthwash Oral Rinse lubricates, moistens, cleans, and provides a coating on oral mucosa.[8,9] Although the Biotène® mouthwash Oral Rinse was initially recommended to improve the oral and pharyngeal environment, anecdotal evidence via a patient's experience appears to indicate that it may be effective in extending the life of voice prostheses. Biotène® mouthwash's effect on *Candida* levels has been studied with respect to oral care and has shown mixed results.[10–12] The fact that Biotène® mouthwash Oral Rinse as an over-the-counter (OTC) product is far less costly than the physician-prescribed nystatin[13] would provide additional benefit.

Despite these potential gains, the effect of Biotène® mouthwash on *Candida* infestation in a TEP has not previously been studied in any prospective trials or observational cohorts. The objective of this randomized, crossover trial was to compare the efficacy of Biotène® mouthwash Oral Rinse with the standard of care, nystatin, for controlling the levels of *Candida* growth in TL patients with a TEP. Our goal was to show that both Biotène® mouthwash and nystatin were superior to basic daily oral care (i.e., brushing teeth, cleaning dentures) for preventing *Candida* growth and to determine whether one treatment was superior to the other.

MATERIALS AND METHODS

This study was conducted in compliance with the Greater Baltimore Medical Center (GBMC) Institutional Review Board requirements. It was a randomized, unblinded, crossover clinical trial comparing nystatin and Biotène® mouthwash for TL patients treated at the Milton J. Dance, Jr. Head and Neck Center (Table I). Laryngectomy patients coming to the center for routine TEP changes were screened and enrolled from May 2007 to June 2010. Inclusion criteria consisted of having a TL with a tracheoesophageal puncture and voice prosthesis and being at least 18 years old. Exclusion criteria included either having any condition that, in the opinion of the head and neck surgeon, could place the patient at undue risk or hamper compliance with the study protocol, or having nonprotocol *Candida* prophylaxis within 2 weeks of study entry. Patients agreeing to participate in the study gave written informed consent.

All patients received both treatments during the course of the trial after an initial run-in with no medication (phase 1). Individuals were randomized 1:1 to the order in which they received the two medications during phase 2 and phase 3 (Table I). At the beginning of phase 1, all patients were given standard instructions for basic oral care and were told to continue this care during all study phases, regardless of the medications used. Instructions on the use of each medication were provided at the beginning of the phase utilizing that medication.

A new TEP was inserted at the start of each phase (1–3). A phase was considered complete once the TEP failed or 3 months of follow-up were completed, whichever came first. Some individuals had a slightly longer follow-up period due to difficulties scheduling a visit for the replacement of TEP (1 patient scheduled at 105 days; another patient scheduled at 121 days).

The effects of Biotène® mouthwash Oral Rinse and nystatin dissipate very quickly in comparison to the duration of each study phase; therefore, a washout period between medications was not used. Individuals using Biotène® mouthwash Oral Rinse generally experience relief of xerostomia quickly with improved oral comfort and moisture, but the effect is only temporary[8,12]; length of effect generally depends on the individual and fluoride topical product used.[9] Two crossover studies including Biotène® mouthwash Oral Rinse did not detect a carryover effect with a 1-week washout period for treatment periods far shorter than in this study.[10,14] The Biotène® mouthwash Oral Rinse is swished for 30 seconds and expectorated. It is not swallowed, as is nystatin,[15] which requires swishing for 5 minutes and then swallowing. The bioavailability of nystatin, the percent of administered drug reaching systemic circulation, is minimal to insignificant.[15] Swallowing the medication, as prescribed for this study, allows for topical application to areas of the gastrointestinal tract that cannot otherwise be reached. Nystatin is excreted in the feces unchanged.[15] Because the drug is not absorbed and is eliminated, the time from dose administration through the gastrointestinal tract to defecation is approximately 24 to 48 hours, depending on the user's bowel habits. After the drug is excreted, no residual effects are present.[15]

The ATOS Medical Provox2 (Hörby, Sweden), 22.5 French (Fr) TEP [16] was selected as the prosthesis to be used in all patients during the study to ensure consistency and comparability of prosthesis type and material. Prosthesis size changes occurred as part of the normal variation in the length of the tracheoesophageal fistula; however, the diameter of the prosthesis was fixed at 22.5 Fr. The Provox2 is an indwelling silicone TEP that can be inserted in situ in the outpatient clinic setting. Studies have shown that the median device life of the Provox2 TEP ranges from 104 to 144 days (3.5 to 4.8 months).[17–19]

In order to measure the *Candida* infiltration, the TEP was removed at the end of each phase and labeled with a deidentified ID and the collection date and time. The TEP was then prepared by the GBMC lab by plating it on a Sabaroud Dextrose (SabDex) agar plate in a container with enough trypticase soy broth to cover the TEP. The container was then covered tightly and shipped refrigerated to the specialty laboratory[20] for final processing. The TEP was then sonicated, and the supernatants from the sonication were vortexed and streaked onto trypticase soy agar plates with 5% sheep blood (for organisms other than yeasts) and SabDex plates (for yeasts only). The original tube was stored at 4°C, the trypticase soy agar plates were incubated aerobically in 5% CO_2 at 37°C for 72 hours, and the SabDex plates were stored at 30°C for 72 hours. The number of organisms grown on the plates was then quantified as colony-forming units (CFUs), the number of viable bacterial cells in a sample per mL.[21] Initial laboratory results reported categories (e.g., >100) as opposed to numeric counts for *Candida* species. The process was corrected, and patients whose prostheses were processed through the laboratory for analysis prior to the correction were asked to repeat the applicable phases of the study.

Outcomes

The primary outcome was the total *Candida* bacteria count (CFUs) on the TEP, which was transformed to the $\log_{10}$ scale for ease of presentation. Measurements that were quantified as "too numerous to count" were assigned a value 10 times higher than the largest observed value for the species.

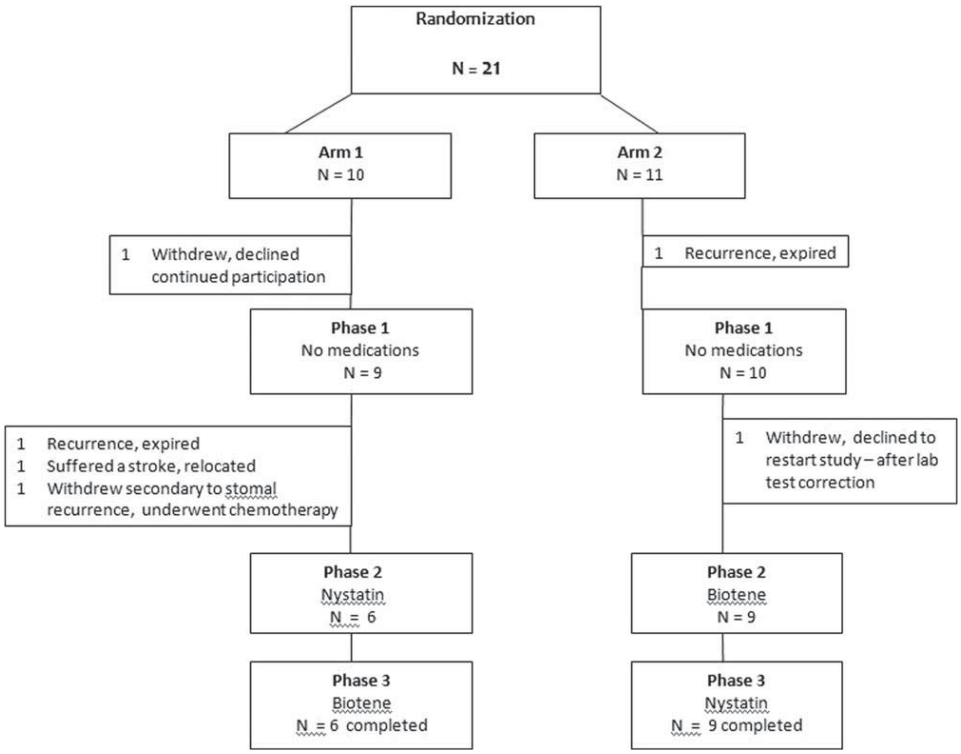

Fig. 1. Study consort diagram.

Secondary outcome measurements included the Functional Assessment of Cancer Therapy Head and Neck (FACT–HN),[22] patient-reported adherence to basic daily oral care and treatment protocol, and the duration of each TEP's life before failure or up to a scheduled 90-day time point. All secondary outcome measurements were collected once during each phase, with the exception of the patient-reported adherence, which was monitored weekly and summarized as the average weekly adherence within each phase.

Statistical Methods

A sample size of 20 patients would provide 80% power to detect an effect size of 0.66, assuming a two-sided type 1 error rate of 0.05. This effect size represents the mean difference in $\log_{10}$ CFUs between two treatments in units of the standard deviation (SD) of the difference.[23] Summary statistics (median, minimum, and maximum) were calculated for each of the treatments and their pairwise comparisons. The Wilcoxon rank-sum test was performed when comparing study arms. The Wilcoxon signed-rank test was performed for comparisons between paired measurements. Analysis cohorts are based on all available data and vary depending upon the outcome studied. Statistical analyses were performed using STATA V12.1 (STATA Corporation, College Station, TX). All tests were two-sided and were considered statistically significant for P values ≤ 0.05.

RESULTS

Study Population

A total of 21 patients were consented for the study, with 10 patients randomized to receive nystatin followed by Biotène® mouthwash Oral Rinse (arm 1) and 11 randomized to receive Biotène® mouthwash Oral Rinse followed by nystatin (arm 2) (Fig. 1). Six patients were excluded from the analyses because they withdrew or expired, including three patients who chose not to repeat study phases. Six patients remained in arm 1 and nine patients in arm 2 (Fig. 1). Fifteen bacteria species were identified on the prostheses, with *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, and *Candida krusei* being the most prevalent species in terms of occurrences and count levels.

Demographic characteristics were compared based upon study completion and, for those who completed the study, based on assigned treatment (Table II). For the 21 consented patients, the mean age was 70 (SD = 12), 91% were males, and the average time from laryngectomy was 55 months (SD = 45). Eighty-six percent had a primary tracheoesophageal puncture, 76% had a history of stricture, and 95% completed radiation therapy. The clinical and demographic characteristics were similar in comparisons between the groups and corresponded to that observed in other studies of laryngeal cancer.[24] However, the missing data level was high (> 33%) for other variables such as history of gastroesophageal reflux disease and whether the patients continued to drink alcohol. The characteristics of those completing the study (n = 15) were similar to that of the group enrolled in the study (Table II).

Total Bacteria Count

Among the 15 patients completing the study, bacterial counts remained high regardless of treatment, with

TABLE II.
Characteristics of Patients by Study Completion Status and Study Arm.

Characteristic	Completed Study		Completed Treatment	
	No	Yes	Arm 1	Arm 2
Number of Patients	6	15	6	9
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)
Age (years)	68 (19)	71 (9)	69 (7)	73 (10)
Laryngectomy to enrollment (months)	36 (47)	63 (44)	58 (32)	64 (44)
	N(%)	N(%)	N(%)	N(%)
Males	5 (83)	14 (93)	6(100)	8 (89)
Primary tracheoesophageal puncture	5 (83)	13 (87)	5 (83)	8 (89)
Hx of stricture	6 (100)	10 (68)	3 (60)	2 (22)
Unknown			*1 (17)*	
Radiation	6 (100)	14 (93)	5 (83)	9 (100)
Chemotherapy	2 (40)	5 (33)	2 (33)	3 (33)
Unknown	*1 (17)*			
XRT-chemotherapy for recurrence	3 (50)	5 (33)	2 (33)	3 (33)
Thyroid	3 (50)	6 (40)	3 (50)	3 (43)
Unknown	*3 (50)*	*2 (13)*		*2 (22)*
Diabetes	1 (17)	2 (13)	1 (17)	2 (29)
Unknown	*3 (50)*	*2 (13)*		*2 (22)*
Hx of smoking	4 (67)	12 (80)	5 (100)	7 (88)
Unknown	*1 (17)*	*2 (13)*	*1 (17)*	*1 (11)*
Currently smoking	2 (33)	1 (7)	5 (100)	8 (89)
Unknown	*1 (17)*	*1 (7)*	*1 (17)*	
Hx of alcohol/any drinking	4 (67)	8 (53)	4 (80)	4 (50)
Unknown	*1 (17)*	*2 (13)*	*1 (17)*	*1 (11)*
Currently drinks	1 (17)	1 (7)	3 (100)	2 (40)
Unknown	*2 (33)*	*7 (47)*	*3 (50)*	*4 (44)*
GERD	2 (33)	8 (53)	3 (100)	5 (100)
Unknown	*4 (68)*	*7 (47)*	*3 (50)*	*4 (44)*

Arm 1: nystatin followed by Biotène® mouthwash Oral Rinse; arm 2: Biotène® mouthwash Oral Rinse followed by nystatin.
N indicates number of patients with the characteristic; % for "unknown" categories based on "number of patients"; % for other characteristics based on the number of patients with responses.
GERD = gastroesophageal reflux disease; Hx = history of; SD = standard deviation; XRT = radiation therapy.

only a few patients dropping below 10^4 CFUs/mL: three patients while using nystatin and two while using Biotène® mouthwash Oral Rinse (Fig. 2). Although all of the drops occurred in the arm that received Biotène® mouthwash Oral Rinse followed by nystatin, there was no significant difference between the measurement of total bacterial count for arm 1 versus arm 2 within any of the three treatments (no medication: $P = 0.95$; nystatin: $P = 0.72$; Biotène® mouthwash Oral Rinse: $P = 0.64$); thus, data from the two arms were combined for the between treatment comparisons. The total bacteria count for the nystatin group was significantly lower than for no medication (median difference [mΔ]: −0.9; range: −9.8 to 1.4; $P = 0.02$; N = 15). Biotène® mouthwash Oral Rinse also lowered the bacterial count (mΔ: −0.3; range: −7.0 to 1.8; $P = 0.22$; N = 15), but this difference was not statistically significant; nor was the difference in bacterial counts between Biotène® mouthwash Oral Rinse and nystatin significantly different (mΔ: 0.2; range: −5.0 to 10.5; $P = 0.22$; N = 15).

Secondary Outcomes

In addition to bacterial counts, we also performed pairwise comparisons of the duration of prosthesis life, adherence, and FACT-HN between the three treatments. Overall, the median lifetime of the prostheses across the 15 patients and three phases was 92 days (95% confidence interval [CI]: 91–NA).

There was no significant difference between the three treatments ($P = 0.52$ to 0.82) for these pairwise comparisons (N = 15). Adherence was measured for both usual oral care and for medication-specific swishing protocols. The oral care adherence was high, with a median adherence of 97% (range: 11% to 100%; N = 12). Although the proportion of individuals with 80% adherence or higher was the same for both groups (83%), the actual adherence was significantly higher for Biotène® mouthwash Oral Rinse than for nystatin (mΔ: 4.6%; range: −0.3% to 10.7%; $P = 0.01$; N = 12). Oral care adherence was not significantly different between the nystatin and no medication phases (mΔ: −1.9%; range: −15.4% to

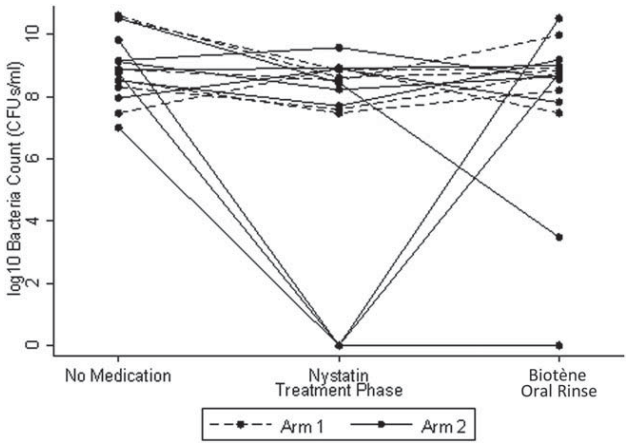

Fig. 2. Pattern of $\log_{10}$ (total bacteria count) across treatment phases for each patient. The dotted lines represent those randomized to receive nystatin followed by Biotène® mouthwash Oral Rinse (arm 1); and the solid lines represent those randomized to receive Biotène® mouthwash Oral Rinse followed by nystatin (arm 2). CFUs = colony-forming units.

49.4%; $P = 0.20$; N = 11) or between the Biotène® mouthwash Oral Rinse and no medication phases (mΔ: 1.6%; range: −11.0% to 53.8%; $P = 0.15$; N = 11). In addition, the medication-specific adherence was high (97%), with Biotène® mouthwash Oral Rinse significantly higher than nystatin (mΔ: 7.6%; range: −1.9% to 16.9%; $P = 0.03$; N = 11). The proportion of patients with 80% or higher adherence was larger with Biotène® mouthwash Oral Rinse (1.00) than with nystatin (0.91). The patients' quality of life was similar for the three treatments ($P > 0.05$ for all subscales); however, the number of individuals with available data for the FACT-HN subscales was low (range: 3 to 8).

DISCUSSION

The focus of this study was to evaluate the ability of nystatin and Biotène® mouthwash Oral Rinse to prevent *Candida* formation of biofilm on a TEP in a laryngectomy patient, as measured by $\log_{10}$ (total bacteria count, CFUs/mL). The impetus for this evaluation was anecdotal evidence that Biotène® mouthwash Oral Rinse helped with preventing *Candida* in one patient. Additional research noted the potential antimicrobial benefits of Biotène® mouthwash Oral Rinse with respect to *Candida*.[11,13] Both therapies had reduced bacteria count as compared to usual care, although the reduction was only statistically significant for nystatin. We were unable to detect a difference between the two medications; however, this may be due to the small number of completers (N = 15). Most of the patients' bacteria counts remained high regardless of medication or nonmedication (Fig. 2). It is also important to note that, unlike the no medication phase, individuals in both the nystatin and Biotène® mouthwash Oral Rinse phases achieved negligible- or reduced-level bacteria counts (N = 3 and N = 2, respectively), the goal of the prophylaxis. The patients with reduced or negligible bacterial counts were all randomized to receive Biotène® mouthwash Oral Rinse prior to nystatin, which raises the question of whether a carryover effect influenced the nystatin results. However, this seems unlikely given the length of the treatment phases (approximately 3 months) and the quick dissipation of either medication's effect. Similarly, it is unlikely that a longer treatment period was necessary to achieve a result because all of the individuals with lower bacteria counts under Biotène® mouthwash Oral Rinse did not have the benefit of another treatment immediately preceding it.

The adherence was significantly higher for Biotène® mouthwash Oral Rinse than for nystatin, which was expected due to the fact that nystatin has a more time-consuming protocol. If there is truly no difference in the anti-*Candida* effect of the two therapies, this fact—along with the lower cost (Biotène® mouthwash Oral Rinse is an OTC product compared to the physician-prescribed nystatin)—would make Biotène® mouthwash Oral Rinse the more attractive treatment option. Also, many laryngectomy patients underwent postoperative radiation therapy resulting in xerostomia, requiring the use of artificial saliva products such as Biotène® mouthwash Oral Rinse. Patients are often familiar with artificial saliva products and may be more accepting of adding Biotène® mouthwash Oral Rinse to the daily oral care regimen. It would also be important to identify demographics and disease characteristics that could identify the conditions when one or the other prophylaxis methods might be more suitable. However, this question must be addressed in future research given the small sample size of this study.

The primary limitation of this study was the small sample size, 15 completers. Hence, only large differences between the two medications would be detectable. Six (29%) patients were excluded from the analysis because they withdrew from the study either for medical reasons (stroke N = 1), expiration (N = 2), or refusal to repeat treatment phases after the correction of the laboratory methods for evaluating bacterial counts (N = 3). Although this represents a large fraction of the consented population, the reasons for withdrawal seem unlikely to be related to the outcomes measured in the study; hence, our primary concern is precision as opposed to bias of our outcome measurements.

CONCLUSION

Nystatin and Biotène® mouthwash Oral Rinse had similar levels of bacterial counts, with nystatin showing a significant improvement over usual oral care. Given the high cost, low benefit, and time-consuming nature of nystatin as an anti-*Candida* treatment, it may be reasonable to consider comparable treatments. Biotène® mouthwash Oral Rinse may be a more favorable option for patients, as reflected in the higher levels of compliance, its lower cost as an easily obtained OTC medication, and the reduced swish time required.

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