Effect of Antibiotics on the Oropharyngeal Flora in Patients With Acne

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Objective: To estimate the prevalence and resistance patterns of *Streptococcus pyogenes* and *Staphylococcus aureus* in the oropharynx of individuals with acne who were using or not using antibiotic therapy.

Design: A cross-sectional study.

Setting: The Dermatology Department of the Hospital of the University of Pennsylvania, Philadelphia.

Patients: Patients with acne.

Main Outcome Measures: Presence or absence of *S. pyogenes* and *S. aureus* in the oropharynx as determined by culture and their resistance patterns to tetracycline antibiotics as determined by agar disk diffusion.

Results: Of 105 patients who participated, 42 were using oral or topical antibiotics and 63 patients were not using antibiotics. Six (10%) of those 63 not using any antibiotics had positive *S. pyogenes* cultures compared with 13 (33%) of those successfully evaluated using antibiotics (n=39) (prevalence risk ratio, 3.5; 95% confidence interval, 1.4-8.6; *P* = .003). A total of 85% of *S. pyogenes* cultures (11/13) from those using antibiotics were resistant to at least 1 tetracycline antibiotic compared with 20% (1/5) from those not using antibiotics (*P* = .01). Of those not using antibiotics, 29% (18/62) had positive *S. aureus* cultures compared with 22% (9/41) of those using antibiotics (prevalence risk ratio, 0.76; 95% confidence interval, 0.38-1.5; *P* = .42). No significant differences in resistance patterns of *S. aureus* were found.

Conclusions: *Streptococcus pyogenes* colonization and resistance in the oropharynx are associated with antibiotic therapy in patients with acne. The clinical and long-term effects of this finding need to be studied further.

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**INDIVIDUALS WITH acne are generally healthy patients often exposed to antibiotics for prolonged periods. They are, therefore, a natural population of patients in whom to study the effects of long-term antibiotic use. It is believed that appropriate but long-term use of antibiotics by patients and physicians has played a role in the development of organisms that are now resistant to multiple antibiotics.**

Importantly, these changes are not always permanent. For example, reductions in the use of antibiotics have been shown to result in subsequent decreases in bacterial resistance in *Streptococcus pyogenes*. Tetracyclines and erythromycin are 2 antibiotics commonly used in dermatological practice for the long-term treatment of acne vulgaris. Studies have shown that *Propionibacterium acnes* and coagulase-negative staphylococci quickly develop resistance to these antibiotics, which may result in therapeutic failure and the propagation of resistance to bacteria in the skin and gastrointestinal flora of close contacts. While the effects of long-term antibiotic use on cutaneous microbial environments in this patient population have been well studied, the effects on noncutaneous surfaces such as the oropharynx (which could be a source of systemic illness) have not.

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Normal oropharyngeal flora include anaerobic (eg, *Peptostreptococcus*) and aerobic species (eg, viridans streptococci). These organisms are rarely pathogenic. *Staphylococcus*, *Streptococcus*, and *Haemophilus* species may also be part of the normal oropharyngeal flora, but they are also more likely to be pathogenic. Few studies have investigated the true prevalence of oropharyngeal colonization by these species in
healthy individuals, but it is presumed to be very low. However, long-term antibiotic use may influence the oropharyngeal colonization and resistance rates of these organisms. For example, the proportion of patients with α-hemolytic streptococci in the oropharynx resistant to penicillin was shown to be 71% to 75% in those receiving oral penicillin compared with 0% in those receiving no antibiotics. Other studies have shown that antimicrobial therapy in patients with acne changes the distribution of bacterial species in the nares.

The goal of this study was to determine the effects of long-term antibiotic administration on the oropharyngeal microbial environment of individuals with acne. The primary objective was to estimate the prevalence of Streptococcus pyogenes and Staphylococcus aureus and the resistance patterns of these organisms to tetracycline antibiotics in the presence or absence of antibiotic therapy.

### METHODS

#### STUDY POPULATION AND DESIGN

A total of 107 male and female patients were recruited to participate in this cross-sectional study. This convenience sample of patients at the Dermatology Department at the Hospital of the University of Pennsylvania was selected without prior knowledge of their antibiotic use. The study was designed to determine the colonization and resistance pattern of S aureus and S pyogenes in the oropharynx of those patients who had been receiving any antibiotic therapy (ie, oral tetracyclines and/or topical) for at least 3 months and those patients who had never used or had not used antibiotics for at least 6 months. Our protocol was reviewed and given approval by the institutional review board of the Hospital of the University of Pennsylvania. All subjects filled out a questionnaire inquiring about the length and type of oral antibiotic use (if any); the type of topical medication (if any), including antibiotics, benzoyl peroxide, and retinoids; acne distribution; an acne self-assessment; and the presence of any upper respiratory tract illness or symptoms during the past 30 days.

#### BACTERIOLOGIC SAMPLING AND ANALYSIS

The oropharynx of subjects was swabbed with a Culturette (BD Diagnostic Systems, Cockeysville, Md) using standard clinical technique. Within 24 hours, the specimen was processed for S aureus and S pyogenes according to ASM (American Society of Microbiology) and NCCLS (National Committee for Clinical Laboratory Standards) guidelines. Swabs were inoculated onto trypticase soy agar with 5% sheep’s blood, Streptococcal Selective agar, and Mannitol Salt agar (BD Diagnostic Systems), streaked for isolation, and incubated at 35°C to 37°C for 24 to 48 hours. Plates were observed for colony morphologic characteristics consistent with those of S aureus and S pyogenes. Golden colonies exhibiting β zones of clearing on blood agar were considered presumptive for S aureus and subcultivated onto blood agar. Identification was confirmed by the positive production of coagulase in the slide and tube coagulase test. β Hemolytic colonies on Streptococcal Selective agar that appeared grayish white were subcultivated onto blood agar. A negative finding in the catalase test, a positive finding in the PYR (L-pyroglutamic acid β-naphthamide) test, and susceptibility to 0.04 U of bacitracin disc confirmed the presence of S pyogenes.

Colonies of confirmed S aureus and S pyogenes were tested for susceptibility to 30 µg of tetracycline, minocycline, and doxycycline by agar disk diffusion (Kirby-Bauer method) using Mueller-Hinton agar plates (with 5% sheep’s blood for S pyogenes). Zones of inhibition were measured and compared with standard values (NCCLS M100-S9) to assign a designation of “susceptible,” “intermediate,” or “resistant” to each antimicrobial agent. Resistance was measured as a function of the diameter in millimeters of the zone of growth inhibition around the antibiotic disk. For S aureus, a specimen was considered resistant to tetracycline or minocycline if the diameter was 14 mm or smaller; indeterminately/intermediately resistant if between 14 and 19 mm; and sensitive if 19 mm or larger. For S pyogenes, a specimen was considered resistant if the diameter was 12 mm or smaller; indeterminately/intermediately resistant if between 12 and 16 mm; and sensitive if 16 mm or larger. For S pyogenes, a specimen was considered resistant to 1 of the 3 antibiotics if the diameter was 18 mm or smaller; indeterminately/intermediately resistant if between 18 and 23 mm; and sensitive if 23 mm or larger. Data on prevalence and susceptibility were stored in a Microsoft Excel 97 spreadsheet (Redmond, Wash).

#### STATISTICAL ANALYSIS

Our primary objective was to estimate the prevalence and resistance of S aureus and S pyogenes in the oropharynx of antibiotic users (ie, oral and/or topical) and nonusers (reference group). Exploratory objectives (or hypothesis-generating objectives) were to estimate S aureus and S pyogenes prevalence and resistance rates in those using only an oral antibiotic, those using only a topical antibiotic, and those using both compared with antibiotic nonusers. Prevalence risk ratios (PRRs) with 95% confidence intervals (CIs) were estimated using 2 × 2 tables and Mantel-Haenszel techniques. For the primary analysis, Pearson χ2 P values were considered significant if they were less than .05. Statistical analyses were performed using Stata 6.0 (Stata Corporation, College Station, Tex). Swabs from 2 subjects were not plated within 24 hours; therefore, they were excluded from analysis. In addition, S pyogenes cultures from 3 subjects (all in the group using any antibiotic) and S aureus cultures from 2 subjects (1 from the antibiotic nonusers and 1 from the group using any antibiotic) could not be interpreted. Therefore, the total numbers of S pyogenes cultures and S aureus cultures included in our analysis were 102 and 103, respectively. Lastly, resistance patterns could not be interpreted in 1 positive S pyogenes culture and 1 positive S aureus culture.

#### RESULTS

The average (SD) age in our study population of 105 individuals was 24.5 (7.5) years, and 70% were female.
Table 2. Prevalence of *Streptococcus pyogenes* and *Staphylococcus aureus* in the Oropharynx of Individuals With Acne Using Antibiotics vs Those Not Using Antibiotics*  

<table>
<thead>
<tr>
<th>Antibiotic Use</th>
<th>S. pyogenes</th>
<th>P Value</th>
<th>S. aureus</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>6/63 (10)</td>
<td>Referent</td>
<td>18/62 (29)</td>
<td>Referent</td>
</tr>
<tr>
<td>Any</td>
<td>13/39 (33)</td>
<td>.003</td>
<td>9/41 (22)</td>
<td>.42</td>
</tr>
<tr>
<td>Oral only</td>
<td>5/18 (28)</td>
<td>.05</td>
<td>4/20 (20)</td>
<td>.43</td>
</tr>
<tr>
<td>Topical only</td>
<td>4/10 (40)</td>
<td>.02</td>
<td>2/10 (20)</td>
<td>.55</td>
</tr>
<tr>
<td>Both oral and topical</td>
<td>4/11 (36)</td>
<td>.01</td>
<td>3/11 (27)</td>
<td>.91</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are number of subjects/potential number of subjects (percentage).

Table 3. Proportion of Tetracycline Class–Resistant *Streptococcus pyogenes* and *Staphylococcus aureus* in the Oropharynx of Individuals With Acne*  

<table>
<thead>
<tr>
<th>Antibiotic Use</th>
<th>S. pyogenes</th>
<th>P Value</th>
<th>S. aureus</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1/5 (20)</td>
<td>Referent</td>
<td>3/17 (18)</td>
<td>Referent</td>
</tr>
<tr>
<td>Any</td>
<td>11/13 (85)</td>
<td>.01</td>
<td>4/9 (44)</td>
<td>.14</td>
</tr>
<tr>
<td>Oral only</td>
<td>4/5 (80)</td>
<td>.06</td>
<td>1/4 (25)</td>
<td>.73</td>
</tr>
<tr>
<td>Topical only</td>
<td>3/4 (75)</td>
<td>.10</td>
<td>1/2 (50)</td>
<td>.29</td>
</tr>
<tr>
<td>Both oral and topical</td>
<td>4/4 (100)</td>
<td>.02</td>
<td>2/3 (67)</td>
<td>.07</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are number of subjects/potential number of subjects (percentage).

Table 4. Number of Antibiotic Users and Nonusers Who Reported the Presence of Upper Respiratory Tract Illness or Symptoms in the Last 30 Days*  

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Nonusers (n = 63)</th>
<th>Users (n = 42)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory illness</td>
<td>15 (24)</td>
<td>13 (31)</td>
<td>.42</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (3)</td>
<td>3 (7)</td>
<td>.35</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Stomach upset</td>
<td>3 (5)</td>
<td>4 (10)</td>
<td>.34</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>.61</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are number (percentage) of subjects.

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Almost daily we are faced with scientific and lay media discussion about the hazards of overprescribing antibiotics and the subsequent effect this practice has on antimicrobial resistance. Individuals with acne are a subset of patients who commonly receive long-term antibiotic therapy, which has generally been considered safe and effective. While common clinical wisdom states that this is true, our findings indicate that caution may be warranted. Those patients in our study who were undergoing any form of antibiotic therapy had more than a 3-fold increase in the prevalence of *S pyogenes* in their oropharynx when compared with those who were not using any antibiotics. In fact, the prevalence of *S pyogenes* in patients using antibiotics (13/39; 33%) was as high as the documented rates in patients with symptomatic pharyngitis, which have ranged from 26.3% to 45% (although this latter rate was for mostly a pediatric population).

The prevalence of *S pyogenes* in the asymptomatic nonantibiotic group was higher than expected for this age group. Reported carrier rates of *S pyogenes* in asymptomatic individuals without acne has ranged from in 1.3% in those older than 10 years to 4.2% in those older than 17 years. Likewise, the prevalence of *S aureus* in the asymptomatic nonantibiotic group was higher than the 5% to 14% carrier rate reported in healthy medical house officers without acne and the 6.5% reported in those older than 10 years. This suggests that patients with acne may have higher baseline rates of bacteria in their oropharynx than those without acne.

It should also be noted that those who were using only oral antibiotics as well as those who were using only
topical antibiotics had similar increases in prevalence when compared with their non–antibiotic-using counterparts, indicating that *S. pyogenes* colonization of the oropharynx is affected by multiple modes of antimicrobial administration. While our primary analysis compared antibiotic users with nonusers, we had expected to observe a trend in subgroup analysis comparing topical only users with oral only users (ie, that only oral antibiotics have an effect on the oropharynx), but we did not. Topical antibiotics, like oral antibiotics, may selectively eliminate certain bacteria and cause shifts in the microbial equilibrium that allow species such as *S. pyogenes* to flourish when they otherwise would be held in check.

However, this does not explain how topical antibiotic administration changes the bacterial colonization of a distant site such as the oropharynx. A possible explanation may be the transfer of organisms or antibiotic to the oropharynx. Potential mechanisms of this transfer might include migration of *S. pyogenes* to the oropharynx either by direct movement via a person's fingers or by another mechanical device such as eating utensils. In fact, the application of topical erythromycin to the forehead has been shown to increase the prevalence and density of erythromycin-resistant coagulase-negative staphylococci not only on the forehead but also in the anterior nares and on the back where it was not directly applied. Translocation of bacteria and/or antibiotic to the oropharynx would seem a less likely occurrence but seems to be a possibility given the results of our study. Another possible explanation for the effect of topical antibiotics on the oropharynx is systemic absorption of these medications. Unfortunately, we did not record the specific type of topical antibiotic therapy our patients were using, but it has been shown that some topical antibiotics may be systemically absorbed. The absorbed antibiotic may be potentially transferred hematogenously to the oropharynx where it could change the microenvironment.

The high rates of tetracycline-resistant *S. pyogenes* in patients using antibiotics is more evidence that antimicrobial administration may have unintended effects on another area of the body. While tetracycline-resistant cutaneous flora has been a well-documented consequence of antibiotic therapy for acne, increased colonization of tetracycline-resistant bacteria in the oropharynx has never been consistently associated with pathogenic disease. Our study is limited in that we only investigated bacterial resistance to tetracycline antibiotics. Previous studies of erythromycin- and tetracycline-resistant cutaneous flora have also shown high rates of cross-resistance to other antibiotics such as penicillin, ampicillin, and clindamycin. Future studies are needed to determine if this is true for tetracycline-resistant oropharyngeal flora.

The implications of tetracycline-resistant bacteria in individuals with acne may not be limited to those using the antibiotics. Relatives of patients using oral tetracyclines have been shown to harbor increased levels of bowel and skin flora resistant to tetracycline and other antibiotics. The effects of long-term antibiotic use on the oropharyngeal flora of relatives have also not been studied, but given the observed effects on bowel and skin flora, the possibility exists for increased resistance of the oropharyngeal flora in close contacts of individuals using long-term antibiotics.

Overall, there were no significant differences in the rates of illness between individuals using antibiotics and those who were not using antibiotics. However, this was a cross-sectional study with retrospective data capture, and as such, it is a poor study design for collection of this type of information. Importantly, *S. pyogenes* is a potentially pathogenic bacteria, and an increased carriage rate of this organism may be undesirable, especially since there have been concerns about the increased likelihood of these organisms carrying toxin-producing phages (eg, phage types responsible for streptococcal toxic-shock syndrome and necrotizing fasciitis). In 1 investigation, the M1 serotype, which is the most common toxin-producing serotype, was identified in 92% of cases of pharyngitis. This raised concern for our patients because a third of them harbored *S. pyogenes* in their oropharynx. Furthermore, some individuals, such as those who are immunosuppressed, may be at higher risk for infection.

The present study provides information on our primary objective, which was to determine the rates of colonization and resistance of 2 bacteria in the oropharynx of individuals with acne who were undergoing and not undergoing antibiotic therapy. While our secondary and exploratory analyses showed differences in colonization and resistance between these 2 groups, it is important to note that this was an initial study and these were not the primary end points of this study. In light of this, our findings should be interpreted carefully and will hopefully generate enthusiasm for further investigation.

Since this was a cross-sectional study, definitive conclusions cannot be drawn about the observed association between antibiotic exposure and increased prevalence of *S. pyogenes*. For example, the possibility exists that individuals with *S. pyogenes* in their oropharynx have more severe acne and therefore require antibiotic treatment. A comparison of colonization rates between our patients with acne and individuals without acne is difficult to make because our study did not include a group of individuals without acne who were not taking antibiotics. However, our data suggest that antibiotic administration increases the colonization and resistance of *S. pyogenes* in the oropharynx of patients with acne. The clinical implications of this finding need to be examined further in a well-designed longitudinal study.

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REFERENCES