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Antibiotics, Acne, and *Staphylococcus aureus* Colonization

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Objectives: To determine the frequency of *Staphylococcus aureus* colonization among patients with acne and to compare the susceptibility patterns between the patients who are using antibiotics and those who are not using antibiotics.

Design: Survey (cross-sectional) study of patients treated for acne.

Setting: Dermatology outpatient office practice

Participants: The study included 83 patients who were undergoing treatment and evaluation for acne.

Main Outcome Measure: Colonization of the nose or throat with *S aureus*.

Results: A total of 36 of the 83 participants (43%) were colonized with *S aureus*. Two of the 36 patients (6%) had methicillin-resistant *S aureus*; 20 (56%) had *S aureus* solely in their throat; 9 (25%) had *S aureus* solely in their nose; and 7 (19%) had *S aureus* in both their nose and their throat. When patients with acne who were antibiotic users were compared with nonusers, the prevalence odds ratio for the colonization of *S aureus* was 0.16 (95% confidence interval [CI], 0.08-1.37) after 1 to 2 months of exposure and increased to 0.52 (95% CI, 0.12-2.17) after 2 months of exposure ($P=.31$). Many of the *S aureus* isolates were resistant to treatment with clindamycin and erythromycin (40% and 44%, respectively), particularly the nasal isolates. Very few showed resistance rates (<10%) to treatment with tetracycline antibiotics.

Conclusion: Unlike current dogma about the long-term use of antimicrobial agents, the prolonged use of tetracycline antibiotics commonly used to treat acne lowered the prevalence of colonization by *S aureus* and did not increase resistance to the tetracycline antibiotics.

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STAPHYLOCOCCUS AUREUS IS A ubiquitous organism that is found in both hospital and community settings.[1,2] While *S aureus* colonizes the skin, it can also be responsible for localized cutaneous infections and life-threatening systemic infections.[1,2] At one time, it was sensitive to many antibiotics and antimicrobial agents. However, because of its ability to adapt to these therapies and become resistant, clinical scenarios now exist in which few therapeutic options remain to treat this organism. Therefore, methicillin-resistant *S aureus* (MRSA) has become commonplace.[1,2]

See Practice Gaps at end of article

Colonization with *S aureus* in general is relatively widespread, with approximately 40% to 50% of the population at large colonized, but, fortunately, in the community, MRSA organisms colonize fewer than 5% of the population.[1] Patients with acne are generally young and healthy and are often exposed to antibiotics for extended periods because long-term antibiotic therapy, oral (eg, tetracycline, erythromycin, trimethoprim-sulfamethoxazole) and/or topical (eg, clindamycin or erythromycin), is a standard of care in the treatment of acne.[3-5] Some of the antibiotics used to treat acne are also among those recommended for the treatment of community-associated MRSA (CA-MRSA) infections.[1,4,6] According to rates among the general population, approximately one-third to one-half of patients with acne are likely to be colonized by *S aureus*.[7] These patients could therefore become a reservoir for CA-MRSA as well as a source of non–CA-MRSA antibiotic-resistant *S aureus* strains.

One cause of the emergence of MRSA may be long-term exposure to antibiotics and antimicrobial agents. For example,

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long-term exposure to antibiotics used to treat acne could create pressure on organisms colonizing the skin, such as *S aureus*, to adapt and to become resistant. The goals of this study were to identify the prevalence of *S aureus* colonization in patients with acne and to assess the resistance phenotypes (ie, those that are susceptible to methicillin, erythromycin, tetracyclines, and trimethoprim-sulfamethoxazole) of *S aureus*. We also sought to compare susceptibility patterns between patients with acne who are using antibiotics and those who are not using antibiotics.

METHODS

POPULATION AND DATA COLLECTION

This was a cross-sectional study involving 83 consecutive consenting patients with clinically diagnosed acne who were actively undergoing treatment at the University of Pennsylvania, Philadelphia. The patients were recruited from the University of Pennsylvania dermatology clinic and approached at the end of their clinic visit. Informed consent approved by the University of Pennsylvania institutional review board was obtained from all participants. No patients were excluded from enrollment in the study.

All participants were asked to fill out a comprehensive survey form; all underwent a visual examination for acne presence and severity; and all had oropharyngeal and nasal swab cultures performed for *S aureus*. The comprehensive survey form assessed age, sex, race/ethnicity, history of acne, history of acne treatment, current or recent antibiotic use, indication for any antibiotic use, duration of antibiotic use, and any past skin or soft-tissue infections attributed to *S aureus*.

Specimens were obtained with a sterile, flocked, polyester, fiber-tipped swab that had been premoistened with the transport solution (Copan eSwab Liquid Amies Transport System; Copan Diagnostics, Corona, California). Samples were taken from the anterior nares by rotating the swab 5 times in each nostril and lightly scraping each quadrant of the nasal mucosa. They were obtained from the oropharynx by swabbing each tonsil, as well as the posterior pharynx, using a different swab from that used in the nose. The specimens were placed in the transport solution and hand-delivered to the laboratory within 4 hours of collection. The swab in the transport system was then vortexed to produce a homogeneous suspension. Next, 100 µL of the suspension was transferred to a selective and differential *S aureus* plate (BBL CHROMagar *S aureus* Medium; BD Diagnostic Systems, Franklin Lakes, New Jersey) and another 100 µL was transferred to a medium for the detection of MRSA (BBL CHROMagar MRSA Medium; BD Diagnostic Systems). The plates were then streaked and incubated at 37°C for up to 48 hours, after which they were read for the presence of *S aureus* as well as for MRSA organisms. For those samples that were found to be positive for *S aureus*, susceptibility testing was performed using disk diffusion testing with clindamycin, erythromycin, trimethoprim-sulfamethoxazole, ciprofloxacin, tetracycline, doxycycline, and minocycline. Standard methods for disk diffusion susceptibility testing, including the detection of inducible clindamycin resistance, were used for antimicrobial susceptibility testing.[8]

EXPOSURE DEFINITION

Primary exposure was defined via the survey form by patient report and chart documentation of at least 1 month of current oral or topical antibiotic use (eg, tetracyclines, erythromycin, clindamycin) for acne treatment. Other exposures were also evaluated as confounding variables, as listed below.

OUTCOME AND CONFOUNDING VARIABLES

Our outcome of interest was a positive *S aureus* culture, whether from the nose or throat, which was then evaluated for methicillin resistance. Confounding was evaluated with respect to age, sex, race/ethnicity, presence and severity of acne, oral and/or topical antibiotic use for acne, and presence of diabetes.

STATISTICAL ANALYSES

The initial analysis for every variable consisted of characterizing the distribution of that factor. Characterization depended on the data and consisted of estimating the mean (standard deviation) for each evaluation. Initial univariate assessments of association, when appropriate, were performed using 2×2 tables and the Mantel-Haenszel statistic. For variables with more than 1 category, $R\times C$ χ^2 statistics was performed. Our primary question was to assess the effect of various risk factors, particularly the use of oral antibiotics for acne, on the development of both methicillin-susceptible *S aureus* and MRSA colonization.

To assess the magnitude of the association of a given risk factor with the outcome of interest, single variable and multivariable logistic regression models were created. Both unadjusted (from a 2-variable logistic model) and fully adjusted (from a multiple-variable logistic model) prevalence odds ratios (pORs) were evaluated, with 95% confidence intervals (CIs). The selection of variables for the multivariable model was based a priori on purposeful selection. All covariates thought to be clinically important were included in the original multivariable model. Additional covariates were added systematically to the model, and if the pOR changed by more than 15%, then that particular covariate was kept for the final multivariate model.[9] Ultimately, variables were removed if they had no effect (<15% change) on the pOR. Values were considered significant at $P<.05$. Statistical analyses were performed with Stata version 11.0 software (StataCorp, College Station, Texas).

RESULTS

The median age in our study population was 24 years (mean [SD] age, 25.6 [9.5] years). There were 51 female and 32 male participants (**Table 1**). Of the 83 total participants, 28 (34%) were using topical antibiotics and 23 (28%) were using oral antibiotics for acne at the time of enrollment. In total, 36 (43%) received either a topical or an oral antibiotic for acne. Nine participants (11%) had received antibiotics for reasons other than acne in the previous 30 days.

Thirty-six of the 83 participants (43%) were colonized with *S aureus*, 2 of the 36 (6%) with MRSA. Twenty of the participants (56%) had *S aureus* solely in their throat; 9 (25%) had *S aureus* solely in their nose; and 7 (19%) had *S aureus* in both their nose and their throat (**Table 2**). Both specimens came from the throat of the 2 patients who were colonized with MRSA (Table 2).

The participants who were currently using oral antibiotics for acne were significantly less likely to be colonized by *S aureus* (5 of 23 [22%]) than those with acne who were not using oral antibiotics (31 of 60

Table 1. Basic Demographics of Study Participants Presented With Sample Size or Percentage of Individuals With That Attribute and the Prevalence Odds Ratios (pORs) for the Likelihood of Colonization With 95% Confidence Intervals (CIs)

Demographic	Sample Size[a]	pOR (95% CI)
Female sex	51 (62)	0.90 (0.37-2.21)
Age, mean (SD), y	25.6 (10)	0.98 (0.94-1.03)
Self-reported race/ethnicity		
White	63 (76)	1 [Reference]
Asian/Pacific Islander	2 (2)	Not reportable
African American/black	18 (22)	1.58 (0.53-4.65)
Hispanic	6 (8)	2.22 (0.58-8.58)
Acne severity grade		
1	9 (11)	1 [Reference]
2	36 (43)	1.79 (0.39-8.29)
3	25 (30)	1.33 (0.27-6.61)
4	11 (13)	1.67 (0.27-10.33)
5	2 (2)	Not reportable

[a] Values other than age are expressed as number (percentage).

[52%]) (pOR, 0.26; 95% CI, 0.09-0.79). Overall, those who used topical antibiotics to treat their acne were also less likely to be colonized by *S aureus* (pOR, 0.30; 95% CI, 0.11-0.82). Overall, the use of any antibiotics (oral or topical) to treat acne was associated with a decreased risk of *S aureus* colonization (pOR, 0.31; 95% CI, 0.12-0.79).

Individual variables were selected a priori to test for confounding. None of the variables added (age, sex, Hispanic lineage, grade of acne severity, or race/ethnicity) had a direct relationship with the colonization rates of *S aureus* (ie, any change in the effect estimate between antibiotic exposure and the presence of *S aureus* was less than 15%). We therefore report only our unadjusted estimates. As a secondary analysis, we looked at how long the patients had been using oral antibiotics and how that related to *S aureus* colonization. The duration of current exposure was dichotomized as oral antibiotic use for 2 or fewer months or for more than 2 months. Of 7 patients who were using oral antibiotics for fewer than 2 months, only 1 (14%) was colonized with *S aureus*. Of 10 patients who were using oral antibiotics for more than 2 months, 3 (30%) were colonized with *S aureus*. When patients with acne who were users were compared with nonusers, the pOR for the colonization of *S aureus* was 0.16 (95% CI, 0.08-1.37) after 1 to 2 months of exposure and increased to 0.52 (95% CI, 0.12-2.17) after 2 months of exposure. A test for trend was not statistically significant ($P=.31$). Many of the *S aureus* isolates were resistant to clindamycin and erythromycin (39.5% and 44.2%, respectively), especially nasal isolates. Low antimicrobial resistance rates (<10%) were detected for all other antibiotics tested (**Table 3**).

In previous studies, we observed an association between oral antibiotic use for acne and the self-report of a "sore throat" in the 30 days prior to the survey.[10,11] We did note a pOR of 1.57 (95% CI, 0.50-4.90) for sore throat among patients exposed to oral antibiotics. This finding was not statistically significant, but the effect estimate was similar to that in our previous studies. Interestingly, those patients who were colonized with *S aureus* were less likely to report a recent history of pharyngitis (pOR, 0.13; 95% CI, 0.03-0.59).

Table 2. Recovery of *Staphylococcus aureus* Based on Location

	Throat		
	Positive	Negative	Total, No. (%)
Nose			
Positive	7	9	**16** (19)
Negative	20	47	**67** (81)
Total, No. (%)	**27** (32)	**56** (68)	**83** (100)

COMMENT

The long-term use of oral antibiotics to treat acne is a common practice, which may have some untoward consequences.[11,12] Concern has been noted in the lay press about the long-term use of antibiotics and the creation of multidrug-resistant microbes.[13] In our study, we found that the overall colonization rates for both *S aureus* (43%) and CA-MRSA (2%) were similar to previous estimates.[7,14] Long-term use of antibiotics decreased the prevalence of *S aureus* colonization by nearly 70% (pOR, 0.31; 95% CI, 0.12-0.79). A decreased rate of colonization was noted with the use of both oral and topical antibiotics. Fewer than 10% of the isolates of *S aureus* were resistant to tetracyclines, the most commonly used antibiotic family to treat acne. Resistance to erythromycin and clindamycin was mostly prevalent among our isolates and was noted in the patients who did and did not use antibiotics. Finally, the ability to identify patients who are colonized by *S aureus* is enhanced by culturing from 2 sites.

Colonization with *S aureus* in general is relatively common in that approximately 40% to 50% of people will be colonized.[1,14,15] However, MRSA colonizes fewer than 5% of patients, and colonization with CA-MRSA is dependent on geographic location and comorbidities.[1,2,16] Prior investigations by Levy et al[7,17] looked at the colonization rates of *S aureus* in young, healthy populations similar to our study population. They looked at both acne and nonacne populations but obtained cultures from the oropharynx only. Our observed oropharyngeal colonization rate of 30% is similar to their findings, as they found a 29% *S aureus* colonization rate in patients with acne and a 26.2% rate in patients without acne, but because they failed to sample the nares, their overall colonization rate was lower.[17] Levy and colleagues also investigated the difference between antibiotic users and nonusers in patients with acne and, indeed, found that antibiotic users had a lower colonization rate (22% vs 29%), but their results were not statistically significant, possibly because they sampled only the oropharynx.[15,18-20] In one study by Levy et al,[7] as well as our current study, the use of antibiotics for the treatment of acne, whether oral or topical, was associated with a decreased *S aureus* colonization rate. In our study, the use of oral antibiotics showed the strongest negative association for

Table 3. Percentage of *Staphylococcus aureus* Recovered by Site Resistance to Tested Antimicrobial Agents

	Clindamycin	Erythromycin	Trimethoprim-Sulfamethoxazole	Ciproflaxacin	Tetracycline	Doxycycline	Minocycline
Nasal, %	59	59	6	6	12	12	12
Throat, %	27	35	0	0	8	4	4

S aureus colonization, with a pOR of 0.26 ($P = .02$; 95% CI, 0.09-0.79).

Assuming that antibiotic resistance is acquired over time, we evaluated the association of time of exposure to the use of oral antibiotics on colonization status. We hypothesized that the rates of *S aureus* colonization would be higher among patients who were receiving longer-term oral antibiotics (>2 months of exposure for their acne treatment) because of antibiotic resistance. A 2-month period was chosen to differentiate between short- and long-term exposure to the antibiotics; however, no statistically significant difference was shown ($P = .31$). A trend may have been established in that 14% of patients who were on an oral regimen of antibiotics for 2 months or less were colonized vs 30% of patients who were on an oral regimen of antibiotics for more than 2 months. However, contrary to what might have been expected based on concerns that microbial resistance increases after long-term antibiotic exposure, at no time was the rate of colonization with *S aureus* greater in patients who were receiving antibiotic therapy than in those who were not receiving antibiotic therapy.

The mechanism responsible for the decreased colonization of *S aureus* noted in this study is likely straightforward (eg, tetracycline antibiotics are active against both *S aureus* and MRSA, and resistance is poorly acquired). An increasing trend in colonization rates was noted over time, but this trend was not statistically significant. The *S aureus* isolates were often resistant to treatment with clindamycin and erythromycin. These isolates were more likely obtained from the patients who were using antibiotics to treat their acne.[14] However, there was no evidence of high levels of resistance to the other antibiotics tested, such as the tetracylines and trimethoprim-sulfamethoxazole. Overall, the patients who were using antibiotics to treat their acne were less likely to be colonized. In the future, prospective studies looking at the colonization status of *S aureus* immediately after the initiation of antibiotic therapy on a weekly basis may help to further elucidate whether there is a point past which *S aureus* colonization is increased with longer duration of use.

It is necessary to evaluate multiple anatomical locations for the presence of *S aureus*. As in other recent studies, *S aureus* colonization was found just in the oropharynx and not in the anterior nares in more than half of the patients in our study.[15,18,19] It was found in the anterior nares but not in the oropharynx in one-fourth of our patients, leaving fewer than 20% of *S aureus*–positive patients with colonization in both the anterior nares and the oropharynx. This finding deviates from a recent study by Nakamura et al,[21] who found that 55.7% of *S aureus* carriers in a pediatric intensive care unit were colonized in both locations. This importance of culturing from both the nares and the throat begs the question of whether Levy et al[7] were able to determine the true carriage rates in their study population. Had we swabbed for *S aureus* solely in 1 location, our results could have been significantly different. The sensitivity of combined nares and throat cultures for MRSA colonization was previously shown to be 90%.[15] Further studies are needed to evaluate the importance of culturing from more than 2 sites.

Our study does have some limitations. It focused on patients who were seen in a dermatology clinic for acne, so our results may not be generalizable to all individuals. We also cannot be certain that we identified all of the patients who were colonized with *S aureus* because we swabbed only the oropharynx and the anterior nares. We did not examine all time points after commencing antibiotic therapy so it is possible that we did not see a time-dependent association that truly exists. We recommend a prospective study that would start before the onset of antibiotic use for acne treatment, with continuous culture attempts at weekly intervals.

In conclusion, this cross-sectional study looked at the prevalence of *S aureus* in a healthy population of individuals with acne. With respect to the use of tetracycline antibiotics, it contradicts previous ideologies that long-term prescribing of antibiotics causes increased prevalence of and resistance to *S aureus*. Specifically, in our study, the prolonged use of antibiotics from the tetracycline class that are commonly used to treat acne lowered the prevalence of colonization by *S aureus* and did not increase resistance to the tetracycline antibiotics. Future research should be conducted with respect to other organisms and antibiotics.

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PRACTICE GAPS

Dermatologists Do Not Yet Fully Understand the Clinical Significance of Antibiotic Use and Bacterial Resistance in Patients With Acne

Since the 1970s, the prevalence of antibiotic-resistant strains of *Propionibacteriums acnes* has increased. There are public health concerns about the development of antibiotic resistance among pathogenic organisms, including *Staphyloccocus aureus*. Furthermore, with the use of tetracyclines in the treatment of methacillin-resistant *S aureus*, concern has been raised regarding the potential contribution of bacterial resistance resulting from the widespread use of tetracyclines in the treatment of skin diseases such as acne.[1]

Despite these data demonstrating resistance, antibiotics are effective in improving acne and are widely used for this chronic condition. Each day, many dermatologists choose between what works best for a single patient (using antibiotics to improve acne) and what works best for population health (avoiding antibiotic resistance). If the antibiotic regimens we prescribe for acne lead to clinically relevant pathogen resistance in our patients or communities and we continue to use those medications when there are alternatives, there is a practice gap. Unless dermatologists keep abreast of the literature, the risk of practice gaps increases. In a cross-sectional analysis of 83 patients with acne, Fanelli et al[2] found that patients using oral or topical antibiotics had a decreased risk of *S aureus* colonization in the nose and throat compared with nonusers and that fewer than 10% of these isolates demonstrated tetracycline resistance. However, a similar study by Levy et al[3] demonstrated a 3-fold increase in *Streptococcus pyogenes* colonization in patients with acne using antibiotics compared with nonusers and a statistically significant increase in the rate of resistance of *S pyogenes* to at least 1 tetracycline antibiotic (85%) compared with a 20% rate of resistance among nonusers. As mentioned by Fanelli and colleagues, closing the gap in our understanding of the effects of antibiotic use on colonization rate and the development of antibiotic resistance among bacteria will require prospective trials in which appropriate culturing techniques for various bacteria are performed before and at various points during antibiotic therapy.

A major practice gap includes a lack of knowledge regarding the ideal duration of antibiotic treatment to maxi-