

# Antibiotic Treatment of Acne May Be Associated With Upper Respiratory Tract Infections

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**Objective:** To determine if the long-term use of antibiotics for the treatment of acne results in an increase in either of 2 common infectious illnesses: upper respiratory tract infections (URTIs) or urinary tract infections.

**Design:** Retrospective cohort study.

**Setting:** General Practice Research Database of the United Kingdom, London, England, from 1987 to 2002.

**Patients:** Patients with a diagnosis of acne.

**Main Outcome Measure:** The onset of either a URTI or a urinary tract infection.

**Results:** Of 118 496 individuals with acne (age range, 15-35 years) who were identified in the General Practice Research Database, 84 977 (71.7%) received a topical or oral antibiotic (tetracyclines, erythromycin, or clindamycin) for treatment of their acne and 33 519 (28.3%)

did not. Within the first year of observation, 18 281 (15.4%) of the patients with acne had at least 1 URTI, and within that year, the odds of a URTI developing among those receiving antibiotic treatment were 2.15 (95% confidence interval, 2.05-2.23;  $P < .001$ ) times greater than among those who were not receiving antibiotic treatment. Multiple additional analyses, which were conducted to show that this effect was not an artifact of increased health care-seeking behavior among our cohorts, included comparing the cohorts of patients with acne with a cohort of patients with hypertension and the likelihood of developing a urinary tract infection.

**Conclusions:** Patients with acne who were receiving antibiotic treatment for acne were more likely to develop a URTI than those with acne who were not receiving such treatment. The true clinical importance of our findings will require further investigation.

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**C**ONCERNS HAVE BEEN EXPRESSED regarding the overuse of antibiotics, which has been associated with the emergence of resistant organisms, an increase in the frequency of human exposure to pathogenic organisms, and an increase in infectious illnesses. Surprisingly, very few studies have been conducted on populations of patients who have actually been exposed to antibiotics for long periods. In fact, there are very few natural models of truly long-term human antibiotic use. If we are to understand the consequences of long-term antibiotic use, then we need a natural model of such use. Acne vulgaris is a model of a disease for which long-term antibiotic use is standard and appropriate therapy.<sup>1,2</sup> Topical erythromycin and clindamycin and oral minocycline, doxycycline, and tetracycline are frequently used to treat acne. Patients with acne therefore represent a unique and natural population in which to study the effects of long-term (>6 weeks)

antibiotic use. While the effects of long-term antibiotic use on cutaneous microbial environments in patients with acne have been well studied, the effects of this therapy on noncutaneous surfaces, such as the oropharynx, which could be a source of systemic illness, have not.<sup>3-9</sup>

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Upper respiratory tract infections (URTIs), such as pharyngitis, are extraordinarily common acute medical problems, primarily of viral origin. In general, about 10% of URTIs are likely due to a bacterial source.<sup>10-13</sup> However, we recently demonstrated that nearly 35% of the patients with acne who were receiving antibiotic therapy and who had no URTI symptoms had group A streptococci in their

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upper airway and that nearly 85% of these strains were resistant to tetracyclines.<sup>4</sup> While the vast majority of URTIs are not of bacterial origin, recent studies have shown that infections may be polymicrobial, in that one organism facilitates the infectious capability of another.<sup>14</sup> Finally, URTIs are usually self-limited acute conditions and are generally of limited consequence. However, they do have huge public health implications because of the large number of individuals who are affected. Two recent survey studies evaluated the loss of productivity in the United States as a result of URTIs, which are defined by pharyngitis, coryza, rhinitis, and low-grade temperatures. Both studies estimated that more than 200 million episodes occur per year in the United States and that the US economy suffers a loss of more than \$25 billion in annual revenue.<sup>15,16</sup>

We recently demonstrated that antibiotic therapy for acne, when given topically and/or orally to young adults, may profoundly affect an individual's likelihood of being colonized with group A streptococci, an organism associated with a common acute medical illness: pharyngitis.<sup>4</sup> Our goal was to determine whether the long-term use of antibiotics for acne results in an increase in a common infectious illness: URTI. To that end, we conducted a retrospective cohort study using the General Practice Research Database (GPRD).

## METHODS

### POPULATION

The GPRD, established in the United Kingdom (UK) in 1987, is a medical records database that general practitioners (GPs) use as the primary means of tracking patient clinical information. The total population in the GPRD exceeds 9 million patients, with more than 35 million person-years of follow-up between 1987 and 2002. About 5% of the UK population are registered in the GPRD, which is broadly representative of the general UK population in terms of age, sex, and geographic distribution. The GPRD, which contains information on diagnoses and medications, was established with the intent of allowing researchers to conduct high-quality epidemiologic studies and has been used in more than 200 peer-reviewed publications. All information is recorded by the GP or a member of the office staff as part of the patient's medical record. Approximately 1500 general practitioners, representing 500 practices across the United Kingdom, participated in the GPRD between 1987 and 2001. The GPs are trained in data entry, and their data are reviewed by administrators at the GPRD to ensure that they are of sufficient quality for research studies.

### COHORT AND EXPOSURE DEFINITION

All study subjects, ranging in age from 15 to 35 years, were seen by a GPRD GP and, for our primary cohort study (exposure was always ascertained before determining the outcome), had a history of acne vulgaris as defined by Reed coding, which is a coding system that is similar to that of the *International Classification of Diseases, Ninth Revision*, but hierarchical in construction. Individuals were classified as having acne and receiving antibiotic treatment for acne if, in addition to a Reed code demonstrating that they had acne, they also had British National Formulary codes consistent with the use of oral erythromycin or an oral tetracycline (eg, doxycycline, minocycline,

oxytetracycline, and tetracycline) for more than 6 weeks or topical erythromycin or clindamycin for more than 6 weeks or a combination of both. Please note that this dosing interval clearly exceeds the recommended dosing used for tetracyclines for the treatment of sexually transmitted diseases and Lyme disease. Patients with Reed acne codes who did not have formulary codes consistent with acne antibiotic use as listed above were considered not exposed to acne antibiotics. All individuals were followed up for 12 months from the time that they qualified for entry into their respective cohorts. We also identified another cohort of patients, in the same age range, consisting of individuals who did not have acne but who did have hypertension. Hypertension was selected because hypertensive individuals frequently receive medical observation but are not generally believed to have an increased risk of infection. The use of this group is important as a means of assessing whether the probability of a URTI diagnosis is related to the frequency of medical observation.

### OUTCOME AND CONFOUNDING VARIABLES

We created 2 statistical models each using a different outcome: the development of (1) a URTI (eg, pharyngitis) or (2) a urinary tract infection (UTI) (a common infection unlikely to be affected by the topical agents that are used to treat acne) within 12 months after the patients were enrolled in the cohorts described above. A validation study has recently shown that while it is difficult to determine the precise bacterial cause of a URTI in the GPRD, determination of the presence or absence of a URTI in general is accurate in the GPRD using Reed codes similar to those used in our study.<sup>17</sup>

Confounding of the association between the outcome variable and the exposure variable (ie, acne antibiotic use) was evaluated with respect to age, year of diagnosis, sex, contraceptive use or contraceptive counseling (only for UTIs), practice, history of diabetes, and history of asthma. We also considered visit frequency for acne (ie, the number of office visits for treatment of acne) and the number of prescriptions for acne antibiotics during the 12 months of observation. We note that, because of issues related to chronology with respect to the exposure and/or the outcome, the covariates used in the model are not strictly what would be called risk factors. In general, the reason behind adjusting for all of these confounders was to investigate whether noted associations were solely the result of more frequent visits to health care providers that might occur when a patient with acne is treated with antibiotics. Therefore, we attempted to rule out this form of ascertainment bias as an explanation for the observed associations of interest.

### STATISTICAL ANALYSES

We described our variables using simple percentages or means with standard deviations. To assess the magnitude of the associations between our acne cohorts and the onset of a URTI or a UTI, we used logistic regression models with a single independent variable in each model as well as with multiple independent variables. The outcome of interest was any URTI or UTI, as described above. If an individual had more than 1 infection of a given type, only the first episode was counted. Both unadjusted (single variable) and adjusted (multiple variable) odds ratios (ORs) were reported with 95% confidence intervals.<sup>18</sup> Adjusted models included all of the confounding variables noted above. As noted in the "Results" section, the number of URTIs among men were so few that statistically proper regression analyses were not possible and are therefore reported for women only. All models exhibited good fit and were evaluated using routine regression diagnostic techniques.<sup>19</sup> Cor-

**Table. Descriptive Variables of Patients With Acne Comparing Those Who Used and Did Not Use an Antibiotic to Treat Their Acne**

Variable	No Antibiotic Used (n = 33 519)	Antibiotic Used (n = 84 977)	P Value
Upper respiratory tract infections, No. (%)	3096 (9.2)	15 185 (18.6)	<.001
Urinary tract infections, No. (%)	1258 (3.8)	3012 (3.5)	.08
Age, mean (SD), y	21.7 (5.7)	21.4 (5.8)	<.001
Female sex, No. (%)	21 507 (64.2)	44 725 (52.6)	<.001
Acne-associated office visits, mean (SD)	2.2 (0.01)	2.8 (0.01)	<.001

relation matrices of the parameter estimates were evaluated for the full model, and excessive collinearity was absent in the models. Adjusted analyses included all of the confounding variables listed above. As secondary analyses, we compared our outcome risks with those among individuals who did not have acne but did have hypertension. We also subdivided acne antibiotic exposure with respect to those patients who used only topical antibiotics, oral and topical antibiotics, or only oral antibiotics.

Statistical analyses were conducted using Stata software (version 8.2; Stata Corp, College Station, Tex). The GPRD data set was manipulated using Oracle and Visual dBase. This study was approved by the institutional review board of the University of Pennsylvania, Philadelphia, and the Scientific and Advisory Board of the Office of National Statistics of the UK, London, England.

## RESULTS

We identified 118 496 individuals with acne between 15 and 35 years old who were entered into the GPRD from 1987 to 2002; 84 977 (71.7%) of them were treated with an antibiotic and 33 519 (28.3%) were not (**Table**). Of those who used antibiotics, 6.1% used topical agents only, 1.3% used oral agents only, and 92.6% used a combination of oral and topical agents. The mean (SD) age was 21.4 (5.76) years among the patients with acne who used antibiotics and 21.7 (5.74) years among those who did not. The median age was 19 years (25th percentile, 17 years; 75th percentile, 26 years) among the antibiotic users and 20 years (25th percentile, 17 years; 75th percentile, 26 years) among the nonusers. Also, 44 725 (52.6%) of the antibiotic users and 21 507 (64.1%) of the nonusers were female. Additional baseline information is shown in the Table. Within the first year of study observation, 18 281 patients (15.4%) had at least 1 URTI that was diagnosed by a GP and 4270 patients (3.6%) had a UTI that was diagnosed by a GP. The OR of a URTI developing within the first year of observation among those using antibiotics compared with those not using antibiotics was 2.15 (95% confidence interval [CI], 2.05-2.23;  $P < .001$ ). The OR of a UTI developing within the first year of observation in women using antibiotics compared with those not using antibiotics was 1.11 (95% CI, 1.03-1.19;  $P = .002$ ).

Using multivariable logistic regression, the OR of a URTI developing within the first year of observation among those using antibiotics compared with nonusers was 2.23 (95% CI, 2.12-2.34;  $P < .001$ ). This model was adjusted by sex, age, year of diagnosis, practice, number of prescriptions for acne antibiotics over the 12 months of observation, number of office visits for acne, history

of diabetes, and history of asthma. The difference between this OR of association of the adjusted and unadjusted model is about 12% and is likely not statistically or clinically important, so we will use the unadjusted OR of 2.15 for the rest of this report.<sup>20</sup> Furthermore, individuals were classified separately into nonusers, users of topical antibiotics only, users of both oral and topical antibiotics, and users of oral antibiotics only. The ORs for the association among the antibiotic users compared with the nonusers were 2.37 (95% CI, 2.12-2.64) (topical only); 1.88 (95% CI, 1.80-1.96) (topical and oral), and 2.75 (95% CI, 2.37-3.18) (oral only). No interactions were noted between URTIs and sex, age, frequency of acne-associated office visits, and use of antibiotics. Finally, to ensure that the increased association of URTIs with acne antibiotic use was not attributable to an increased frequency of office visits, we compared the rate of URTIs among patients aged 15 to 35 years in the GPRD with another underlying diagnosis requiring somewhat frequent care, ie, hypertension among those aged 15 to 35 years in the GPRD who did not have a diagnosis of acne. The rate of URTIs among those in the hypertension cohort was 7.9% (1653 cases of URTI among 20 871 individuals with hypertension). When the cohort with the antibiotic nonusers was compared with the hypertension cohort, after age and sex were adjusted for, the OR was 0.97 (95% CI, 0.93-1.01), and when the cohort with the acne antibiotic users was compared with the hypertension cohort, the OR was 2.12 (95% CI, 2.00-2.27).

Because of the rarity of UTIs in men (33 men who used antibiotics had a UTI), multivariable regression models were not possible for them. Using multivariable logistic regression for women only, the OR of a UTI developing within the first year of observation among those with acne antibiotic users compared with nonusers was 1.10 (95% CI, 1.01-1.19;  $P = .02$ ). This model was adjusted for sex, age, number of prescriptions for acne antibiotics over the 12 months of observation, year of diagnosis, number of office visits for acne, contraceptive use, history of diabetes, history of hypertension, and history of asthma. The OR of association changed minimally compared with the unadjusted model, indicating that confounding was unlikely to be important.<sup>20</sup> Also, the magnitude of either the adjusted or the unadjusted OR is unlikely to be of clinical importance. This lack of clinical and statistical association comparing acne antibiotic users and nonusers was confirmed when we compared the antibiotic users with those with hypertension, which again revealed no association with UTIs (OR, 1.09; 95% CI, 0.91-1.30;  $P = .34$ ).

Based on discussions in the lay and scientific press, it would be appropriate to hypothesize that individuals who are on a long-term regimen of antibiotics might be more susceptible to infections. Although this hypothesis seems to be discussed as if it were a fact, it has not truly been tested. Our study was designed to evaluate this hypothesis by using a frequently published patient record database to determine whether there is an association between long-term antibiotic therapy for an appropriate medical reason and an infectious complication in basically healthy individuals. The antibiotics that are used to treat acne, which are primarily erythromycin, the tetracyclines (eg, minocycline, doxycycline, oxytetracycline, and tetracycline), and clindamycin, are no longer frequently used to treat bacterial causes of URTIs. However, URTIs are among the most frequent illnesses noted in our target population: individuals aged 15 to 35 years. In our study, we noted that the odds for those with acne who are using antibiotics are about 2 times greater with respect to developing and seeking medical care for a URTI than for those with acne who are not using antibiotics. This effect is unlikely to be attributable solely to an increased frequency of medical care being sought by individuals with acne who are receiving antibiotics, because this effect was not confounded by several variables that we used as measures of the likelihood of physician visits. The effect also persisted regardless of the mode of administration of the antibiotic. As expected, no association was noted for UTIs, another common infection. Finally, the odds of a URTI developing in a patient with acne who is receiving antibiotic therapy were also 2 times greater than in those with hypertension.

While it might seem odd that the topical application of an acne antibiotic could have an effect on the development of a URTI, studies have previously shown that topical antibiotics used to treat acne do have an effect on cutaneous flora distant from their site of application, as well as on the colonization of bacteria in the nares, a commonly noted reservoir for gram-positive bacteria, and even on other persons closely situated to the acne antibiotic user.<sup>5,6,8,9</sup> Also, in a cross-sectional study, we recently demonstrated that the oropharynx is more prone to be colonized with group A streptococci in individuals who are receiving topical or oral antibiotics for acne than in individuals with acne who are not receiving antibiotics.<sup>4</sup> It may seem counterintuitive that individuals who are using antibiotics would have such an increased risk for developing a URTI when so few URTIs are attributable to bacterial causes. First, the frequency of bacterial URTIs may not be correct for our target age group, in that several recent studies have indicated that the rates of oropharyngeal colonization by pathogenic bacteria may be higher than previously reported.<sup>4,12,13,21,22</sup> Second, some studies have demonstrated that bacterial colonization can influence cell surface receptors such that scenarios have recently been described showing how one organism (whether viral or bacterial) could have an effect on the infectivity of another.<sup>14,23,24</sup> Finally, our analysis is overly conservative and should bias our results toward the null in that the patients with any exposure to antibiotics were classified as antibiotic users when, in fact, their overall exposure during

our year of observation may have been for no longer than 6 weeks.

As with all retrospective database cohort studies, our study does have limitations. First, with respect to URTIs, we do not know if our subjects truly had a URTI. This issue has been previously investigated in the GPRD, and the diagnosis of a respiratory tract infection is likely accurate, albeit ascertainment of a bacterial source is not.<sup>17</sup> Importantly, we are not claiming that the association that we note is attributable to bacterial pharyngitis. We have found only that there is an association between the use of antibiotics for the treatment of acne and physician coding an office visit for pharyngitis. The plausibility of this association as a causal inference has not been established, although, as noted above, mechanistically polymicrobial infections in humans are likely and may be the mechanism in our study.<sup>14</sup> While we do know with certainty that the patients in the non-acne antibiotic group did not receive an acne antibiotic, as we defined that group of medications, it is possible that other oral antibiotics, such as sulfa-based antibiotics and penicillins, may have been used to treat acne.<sup>2,25</sup> These antibiotics are not as commonly used to treat acne as the acne antibiotics that we used, but they could have contaminated our nonantibiotic group and biased our results toward the null. Also, individuals in our study may have used antibiotics for other illnesses, and an individual's home environment may have been associated with varying risks for infectious illnesses. However, we have no reason to suspect that these issues would have been different between the cohorts that we studied. Our study also potentially suffers from confounding by indication. The use of oral antibiotics to treat acne is usually reserved for patients with moderate to severe disease, and it is likely that those with the most severe disease are treated with antibiotics for the longest period.<sup>2</sup> It would not be possible in our current study to differentiate the severity of acne from the need for antibiotic therapy and, therefore, the associations that we noted in our study.

In summary, acne is a condition that affects adolescents and young adults. Based on US population data, about 2 million individuals per year in the United States have severe enough acne to require treatment, and acne accounts for 5 to 6 million physician office visits every year.<sup>1,26</sup> Therapy frequently continues for more than 6 months.<sup>1</sup> In this study, we have shown that the odds of a URTI developing among individuals who use an antibiotic to treat acne is about 2 times greater compared with those who do not use an antibiotic. The true clinical importance of our findings, in which patients and practitioners need to balance the risk of these infections with the benefits that patients with acne receive from this therapy, will require further investigation. However, patients with acne represent an ideal model in which to study the long-term effects of antibiotic therapy, the risks associated with colonization, and the risks of increasing resistance among bacterial pathogens exposed to antibiotics during treatment.

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## REFERENCES

1. Stern RS. Medication and medical service utilization for acne 1995-1998. *J Am Acad Dermatol.* 2000;43:1042-1048.
2. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2003; 49(suppl):S1-S37.
3. Marples RR, Kligman AM. Ecological effect of oral antibiotics on the microflora of human skin. *Arch Dermatol.* 1971;103:148-153.
4. Levy RM, Huang EY, Roling D, Leyden JJ, Margolis DJ. Effect of antibiotics on the oropharyngeal flora in patients with acne. *Arch Dermatol.* 2003;139:467-471.
5. Vowels BR, Feingold DS, Sloughfy C, et al. Effects of topical erythromycin on ecology of aerobic cutaneous bacterial flora. *Antimicrob Agents Chemother.* 1996; 40:2598-2604.
6. Leyden JJ, McGinley KJ, Cavalieri S, Webster GF, Mills OH, Kligman AM. *Propionibacterium acnes* resistance to antibiotics in acne patients. *J Am Acad Dermatol.* 1983;8:41-45.
7. Sanders CC, Sanders WE, Harrowe DJ. Bacterial interference: effects of oral antibiotics on the normal throat flora and its ability to interfere with group A streptococci. *Infect Immun.* 1976;13:808-812.
8. Leyden JJ. Effect of topical benzoyl peroxide/clindamycin versus topical clindamycin and vehicle in the reduction of *Propionibacterium acnes*. *Cutis.* 2002; 69:475-480.
9. Mills O Jr, Thornsberry C, Cardin CW, Smiles KA, Leyden JJ. Bacterial resistance and therapeutic outcome following three months of topical acne therapy with 2% erythromycin gel versus its vehicle. *Acta Derm Venereol.* 2002;82: 260-265.
10. Kaplan EL, Top FH Jr, Dudding BA, Wannamaker LW. Diagnosis of streptococcal pharyngitis: differentiation of active infection from the carrier state in the symptomatic child. *J Infect Dis.* 1971;123:490-501.
11. Kaplan EL. Clinical guidelines for group A streptococcal throat infections. [comment]. *Lancet.* 1997;350:899-900.
12. Kaplan EL, Wotton JT, Johnson DR. Dynamic epidemiology of group A streptococcal serotypes. *Lancet.* 2002;359:2115-2116.
13. Collins M, Fleisher GR, Fager SS. Incidence of beta hemolytic streptococcal pharyngitis in adolescent with infectious mononucleosis. *J Adolesc Health Care.* 1984; 5:96-100.
14. Brogden AM, Guthmiller JM, Taylor CE. Human polymicrobial infections. *Lancet.* 2005;365:253-255.
15. Bramley TJ, Lerner D, Sames M. Productivity losses related to the common cold. *J Occup Environ Med.* 2002;44:822-829.
16. Feudrick AM, Monto AS, Nightengale B, Sarnes M. The economic burden of non-influenza-related viral respiratory tract infection in the United States. *Arch Intern Med.* 2003;163:487-494.
17. Metlay JP, Kinman J. Failure to validate pneumococcal pneumonia diagnoses in the General Practice Research Database [abstract]. *Pharmacoepidemiol Drug Saf.* 2003;12:S163.
18. Harrell FE Jr. *Regression Modeling Strategies.* New York, NY: Springer-Verlag NY Inc; 2001.
19. Hosmer DW, Lemeshow S. *Applied Logistic Regression.* 2 ed. New York, NY: John Wiley & Sons Inc; 2000.
20. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol.* 1989;129:125-137.
21. Haukness HA, Tanz RR, Thomson RB Jr, et al. The heterogeneity of endemic community pediatric group A streptococcal pharyngeal isolates and their relationship to invasive isolates. *J Infect Dis.* 2002;185:915-920.
22. Bisno AL, Kaplan EL. Appropriate use of antibiotics: pharyngitis. *Ann Intern Med.* 2002;136:489-490.
23. Gunn GR, Zubair A, Peters C, Pan ZK, Wu TC, Paterson Y. Two *Listeria monocytogenes* vaccine vectors that express different molecular forms of human papilloma virus-16 (HPV-16) E7 induce qualitatively different T cell immunity that correlates with their ability to induce regression of established tumors immortalized by HPV-16. *J Immunol.* 2001;167:6471-6479.
24. Dietrich G, Kolb-Maurer A, Spreng S, Scharf M, Goebel W, Gentschev I. Gram-positive and gram-negative bacteria as carrier systems for DNA vaccines. *Vaccine.* 2001;19:2506-2512.
25. Oberemok SS, Shalita AR. Acne vulgaris, II: treatment. *Cutis.* 2002;70: 111-114.
26. Stern RS. Dermatologists and office-based care of dermatologic disease in the 21st century. *J Invest Dermatol Symp Proc.* 2004;9:126-130.

## Announcement

### Trial Registration Required

As a member of the International Committee of Medical Journal Editors (ICMJE), *Archives of Dermatology* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as <http://ClinicalTrials.gov>). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of *Archives of Dermatology* (2005;141:76-77). Also see the Instructions to Authors on our Web site: [www.archdermatol.com](http://www.archdermatol.com).