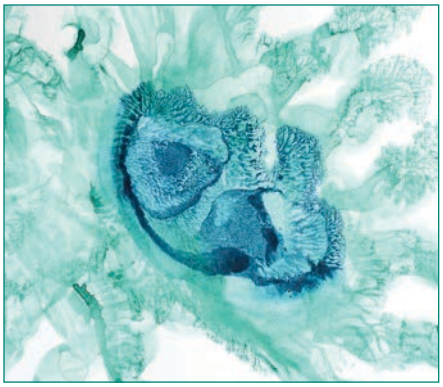

ORIGINAL RESEARCH

Patient Awareness of Antimicrobial Resistance and Antibiotic Use in Acne Vulgaris

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J Clin Aesthet Dermatol. 2019;12(6):30–41

ABSTRACT

Background: Antibiotic resistance presents a threat to public health. In dermatology, antibiotics are used extensively for the treatment of acne, sometimes for extended periods. Thus, awareness of antibiotic resistance among dermatology patients is relevant in clinical practice. **Methods:** An online survey assessed antibiotic resistance awareness in adults with acne (n=809) and the parents of adolescents with acne (n=210).**Results:** More than 80 percent of subjects said that they were "somewhat familiar" or "very familiar" with antibiotic resistance. Overall, 86 percent of the survey respondents identified the correct definition of antibiotic resistance, with parents more likely than their children to choose the proper definition of resistance, as follows: "When antibiotics and/or antibacterials are used for a period of time, the infectious organism adapts to them and becomes immune, resulting in less effective treatment" (95% confidence interval). Among subjects who might have been prescribed antibiotic treatment for their acne, including individuals that reported antibiotic treatment and individuals that were not sure, 76.9 percent reported that they would be very or extremely likely to use effective antibiotic-free options if given the opportunity. More than 90 percent of people with acne and their parents agreed that healthcare providers should do more to educate patients about antibiotics and antibiotic resistance. **Conclusions:** This survey indicated that patients with acne and their parents think more should be done to educate the public about about the potential risks associated with antibiotic use and the availability of antibiotic-free treatment options. Discussions with patients about antibiotic therapies, antibiotic resistance, and alternative therapies represent areas of opportunity for healthcare providers in dermatology.

KEYWORDS: Acne, antibiotic resistance, antibiotics

Antibiotic resistance is an emerging threat to public health, a concern that has recently been highlighted in the medical and general public literature.[1–3] Despite the widespread interest in the topic of antibiotic stewardship, limited data are available describing public awareness and understanding of the issues surrounding antibiotic resistance. Dermatology patients are often prescribed antibiotic therapies, both for short-term infections and for chronic inflammatory dermatoses.[4] Patients with acne and rosacea, together making up approximately 20 percent of the United States (US) population, are frequently offered or prescribed antibiotic therapies.[5] These conditions are often treated with tetracycline-class antibiotics, or, in the case of acne, topical clindamycin, both of which are also used systemically in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA).[4,6,7] More generally, in 2013, in the US alone, dermatological diseases accounted for 5.8 million oral antibiotic prescriptions and 3.5 million topical antibiotic prescriptions.[8] Because the number of dermatology patients exposed to antibiotic therapies is so extensive, they represent an excellent subpopulation in which to study antibiotic resistance awareness.

With at least 50 million people with acne living in the US, acne vulgaris (AV) is one of the most common skin diseases in the country.[9–11] Though AV is most prevalent among adolescents, it can occur at any age, often starting in the preteen years and persisting into adulthood.[11,12] AV is an inflammatory cutaneous disorder that can affect the face, back, and/or chest, presenting with any combination of comedones (open or closed), papules, pustules, and/or nodules.[9] The traditional understanding of acne pathophysiology has included four primary components: : abnormal keratinization and follicular desquamation, changes in sebum composition and/or production, proliferation of *Cutibacterium acnes* (*C. acnes*, formerly called *Propionibacterium acnes*), and multiple pathways of inflammation.[13,14] Additionally, hormonal factors (such as increased androgens or corticotropin-releasing hormone) can contribute to acne pathophysiology by promoting alterations in the composition and quantity of sebum.[15–17] Advances in the understanding of acne pathophysiology have revealed inflammation to be a common contributor across all forms of acne.[13,14,18–22] While the contribution of *C. acnes* to acne pathology seemingly justifies the widespread use of antibiotic treatment, the precise role of *C. acnes* in acne pathogenesis remains unclear.[23,24] Some strains of *C. acnes* are proinflammatory and might activate receptors of the innate immune system, which, in

FUNDING: This study was funded by Galderma Laboratories, LP.

DISCLOSURES: Drs. Del Rosso, Rosen, and Palceski are consultants and investigators for Galderma. Dr. Del Rosso has served as a research investigator and speaker for Galderma. Dr. Rueda was an employee of Galderma at the time this article was written.

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turn, lead to the activation of inflammatory cytokine cascades.[19–21] Furthermore, increased antimicrobial peptide levels have been observed in AV, which might be the result of *C. acnes* proliferation or *C. acnes*-induced changes in sebum levels and composition.[25–27] Alterations in sebum and *C. acnes* within the pilosebaceous unit also appear to contribute to hyperkeratinization and comedone formation.[14] However, despite the apparent contribution of *C. acnes* to AV, the bacterium is commensal, with proliferation of proinflammatory strains contributing to host response patterns that take part in the development of AV lesions. AV is not generally considered communicable.[14,28–31]

Therapies used by clinicians to initiate treatment of AV include topical retinoids (e.g., adapalene, tretinoin, tazarotene) and antimicrobial agents (e.g., benzoyl peroxide or topical/oral antibiotics); the selection of agents is correlated with the severity of AV, often with a combination therapy approach.[9,10,14,32] Fixed combination topical treatments provide convenience, with efficacy and safety established in clinical studies and with real-world use.[33–38] Additionally, therapies for adult women with AV can include combination oral contraceptives and oral spironolactone.[9,14,32,39] With increasing severity, recommendations from the Global Alliance and American Academy of Dermatology include the addition of oral antibiotics or oral isotretinoin; however, the use of topical and oral antibiotics in acne therapy has become more scrutinized in recent years due to global concerns regarding antibiotic resistance.[4,6,7,9,10,40–42] Dermatologists prescribe a relatively higher percentage of antibiotics (3–5% of all antibiotics prescribed across specialties) compared to other types of physicians, with up to two-thirds of these prescriptions being written for AV and, therefore, presumably requiring an extended course of therapy.[4,8] Because the length of exposure to antibiotics is one of the important contributing factors in the emergence of antibiotic resistance among exposed bacteria, the judicious use of such agents in dermatology is one of many steps that can be taken to mitigate the development of antibiotic-resistant organisms.[4,6,7,41–43]

The progressive emergence of bacterial resistance is one potential consequence of widespread clinical antibiotic use. While prophylactic antibiotic use in livestock is considered to be a major factor contributing to the rise in microbial resistance, clinical antibiotic use also contributes to an environment fostering the development of resistance.[1,4,6,44] Additionally, bacterial resistance is not the only inevitable consequence associated with the clinical use of antibiotics. Both topical and oral antibiotics have been associated with changes in the human microbiome (the vast array of commensal, symbiotic, opportunistic, and pathogenic microorganisms that reside on and within the human body).[41,45] Topical antibiotics alter the cutaneous microbiota, leading to resistance patterns, even at anatomical sites distal to the site of application. For example, alterations in bacterial flora within the anterior nares and at remote cutaneous sites have been observed following facial application of antibiotics.[46,47] Likewise, oral antibiotics can lead to changes in the gastrointestinal (GI) microbiome. This can lead to alterations in commensal competition and flora balance, as well as to the creation of reservoirs of antibiotic resistance within specific microbiota. Systemic antibiotic treatment can also result in opportunistic infection by *Clostridium difficile* (*C. difficile*) and contribute to GI-related adverse events.[9,43,45]

The impact of antibiotic use and misuse on the emergence of antibiotic resistance, both in the US and worldwide, has led the US Centers for Disease Control and Prevention (CDC) to focus on educational and public awareness measures to support antibiotic stewardship. Among the resistant organisms that can result from antibiotic therapy, carbapenem-resistant *Enterobacteriaceae*, drug-resistant *Neisseria gonorrhoeae* (*N. gonorrhoeae*) (over half of which display resistance to tetracycline), multidrug-resistant *Pseudomonas aeruginosa*, MRSA, and *C. difficile* have been identified as urgent threats by the CDC.[48] Worldwide, many common bacteria, such as *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*), are exhibiting high rates of resistance, negatively impacting available treatments for common infections, including urinary tract infections and pneumonia.[49]

The current study measured the attitudes toward and awareness of antibiotic resistance among adults with AV and the parents of children/adolescents with AV. Among respondents, this study assessed their experience with antibiotics and antibiotic-free acne treatments, awareness of and experience with superbugs (i.e., strains of bacteria resistant to antibiotics), and agreement with potential actions to limit the future impact of antibiotic resistance.

METHODS

Subjects. The study included survey data from 1,019 subjects. Respondents belonged to one of two groups: 1) People aged 17 to 40 years who had received a prescription treatment (oral or topical) for AV in the previous year (n=809); and 2) parents of children or adolescents (aged 9–17 years) who had received a prescription for AV in the past year (n=210). All subjects were US residents. Participants were required to agree to release contact information in the case of adverse events and/or product-quality complaints. Respondents were obtained from a propriety American Consumer Opinion Panel (Decision Analyst, Arlington, Texas). From the panel, 183,037 panelists were invited to undergo screening, 14,224 completed the screening, and 1,019 qualified and completed the full survey. Patients who met inclusion criteria were informed that individual responses would be anonymous and confidential and were invited to complete the survey by clicking continue.

Survey design. Subjects were surveyed online through Decision Analyst, and included a nationally representative (US, including Alaska and Hawaii) sample of patients with AV, as well as parents of adolescent patients with AV. The survey sections utilized in this study included three main categories of questioning:

1. Demographic questions (employment status, marital status, household income, ethnic background, and educational level; five questions)
2. Study eligibility determination (age, sex, recent diagnoses, and treatments prescribed; 12 questions, some with multiple parts)
3. Assessment of awareness of antibiotic resistance and superbugs, experiences with antibiotic and antibiotic-free therapies for AV, emotional impact of AV, and agreement with potential actions to increase awareness and limit the impact of antibiotic resistance (29 questions, some with multiple parts).

The survey included a combination of free-response and aided (prompted, recognition-

TABLE 1. Study subject demographics (N=1,019)

DEMOGRAPHIC	PATIENTS, % (n=809)	PARENTS OF PATIENTS, % (n=210)
Sex		
Male	34.2	23.8
Female	65.8	76.2
Age (years)		
9–17	0	100*
17–24	34.4	0
25–29	27.4	0
30–34	22.4	0
35–39	15.8	0
Geographical region		
South	37.8	40.5
Midwest	22.4	16.2
Northeast	20.9	20.5
West	18.9	22.9
Race/ethnicity		
Caucasian or White	59.6	79.5
Hispanic or Latin American	12.7	9.5
Asian or Pacific Islander	8.7	2.9
African American or Black	6.9	5.7
Multiethnic or multicultural	2.0	1.4
American Indian, Eskimo, or Aleut	0.6	0.5
Other ethnic background	0.0	0.5
Household income		
Under $10,000	5.2	2.4
$10,000–$24,999	10.6	7.1
$25,000–$49,999	26.0	18.1
$50,000–$99,999	41.9	46.7
$100,000–$149,999	12.4	19.5
$150,000–$199,999	2.5	3.3
$200,000 or more	1.5	2.9

*Age of children/adolescent patients represented by parents

based) response questions. For the multipart questions, depending on responses, some respondents were exempted from subsequent nonapplicable questions. Survey results were descriptively tabulated and 90 and 95 percent confidence intervals (CIs) were used to identify significant differences between the groups.

RESULTS

Subject demographics. Subject demographics are presented in Table 1. The majority of respondents were women (65.8% of adult patient respondents and 76.2% of parent respondents) and identified as Caucasian or white (59.6% of adult patients and 79.5% of parents). The mean household income of adult patient respondents was $65,200, and the mean household income of parent respondents was $78,900. Respondents resided throughout the US.

Respondent understanding of antibiotic overuse and efficacy. The majority of respondents had a basic understanding of antibiotic resistance, with parents more likely than adult patients to correctly define antibiotic resistance as "when antibiotics and/or antibacterials are used for a period of time, the infectious organism adapts to them and becomes immune, resulting in less effective treatment." This response was chosen by 91.4 percent of parents versus 85.4 percent of adult patients (significantly different at 95% confidence interval (CI); Figure 1).

More than 80 percent of respondents said that they were at least somewhat familiar with the topic of antibiotic resistance (Figure 2A). Antibiotic resistance awareness was high among both sexes, although some differences and trends were seen in response rates. A greater percentage of male patients with AV, compared to female patients (significant at 95% CI), and a greater percentage of female parents, compared to male parents (not significant [NS]), indicated that they were very or somewhat familiar with antibiotic resistance (Figure 2B). Antibiotic resistance awareness was high among all age groups, with self-reported awareness among patients with AV increasing with age (Figure 2C). Among both patients and parents, the most frequently reported first source of antibiotic resistance information was a physician or medical professional. In contrast, less common sources of "first awareness," including the news media or online sources, were reported at different rates between the two groups of respondents (Table 2).

Familiarity and concerns around oral versus topical antibiotics. Overall familiarity with the risk of antibiotic resistance resulting from the use oral antibiotics was high. More than 84 percent of respondents agreed that one can develop antibiotic resistance from oral antibiotics. Agreement was similar among patients (83.8%) and parents (86.5%). Agreement that one can develop antibiotic resistance from topical antibiotics was lower, at an average of 62.1 percent of patients (62.7% patients, 59.9% parents). There was a significant difference (at the 95% CI) in respondent knowledge concerning the consequences of antibiotic overuse when patients and parents were compared: 36.7 percent of patients versus 21.4 percent of parents responded that they "did not know overuse of antibiotics could increase (my) risk for an antibiotic-resistant infection." Men (both patients and parents) were more likely to agree with this statement than women (significantly different at 95% CI).

The majority (56.2%) of respondents somewhat or completely agreed with the assertion that oral antibiotics are more likely to cause antibiotic resistance when compared to topical antibiotics used for the treatment of skin disorders. Only 31.2 percent of respondents agreed with the opposing statement, that topical antibiotics are more likely to cause antibiotic resistance when compared to oral antibiotics used for the treatment of skin conditions such as AV and rosacea.

Perceptions of antibiotic efficacy in acne. A very small percentage of respondents (5.4%) agreed with the assertion that AV can only be treated by antibiotics, with a significantly greater percent of patients than parents thinking this to be true (6.1% vs. 2.9%, respectively, significant at 95% CI). Interestingly and surprisingly, the majority (74.2%) of respondents somewhat or completely agreed with the statement: "for acne, I would prefer to use (or have my children use) an effective antibiotic-free prescription treatment instead of a full-dose antibiotic."

More than half (53.9%) of study subjects responded that they (or their children) were prescribed an antibiotic for AV during (approximately) the past year. Only 31.7 percent of antibiotics users (or those who were not sure whether they were prescribed an antibiotic)

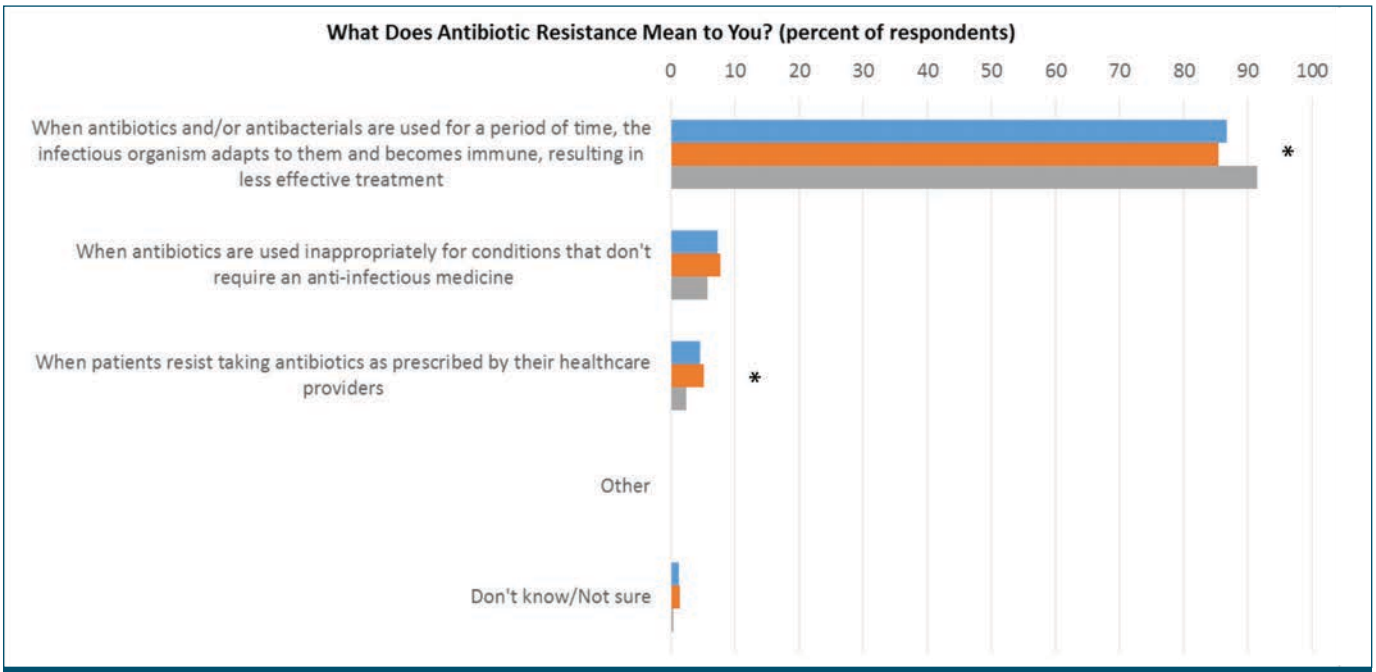

FIGURE 1. Percent reponses to the question"What does antibiotic resistance mean to you?" broken down by aided definitions (95% confidence interval)

TABLE 2. Source of first awareness of antibiotic resistance (N=1,019)

SOURCE	PATIENTS, % (n=809)	PARENTS OF PATIENTS, % (n=210)
Physician/ medical professional	23.3	31.4*
Dermatologist	9.8*	3.4
Pediatrician	4.4	17.4*
Pharmacist	5.3*	1.9
News/media	13.2	21.3*
Online	12.4*	4.8
Friends/family/ neighbors (WOM)	11.1*	6.8
School/college	9.3*	1.9
Social media	2.6	2.4
Other	1.8	2.4
Don't recall	6.7	6.3

WOM: Word of mouth
*Significantly higher than the other group at the 95% confidence interval

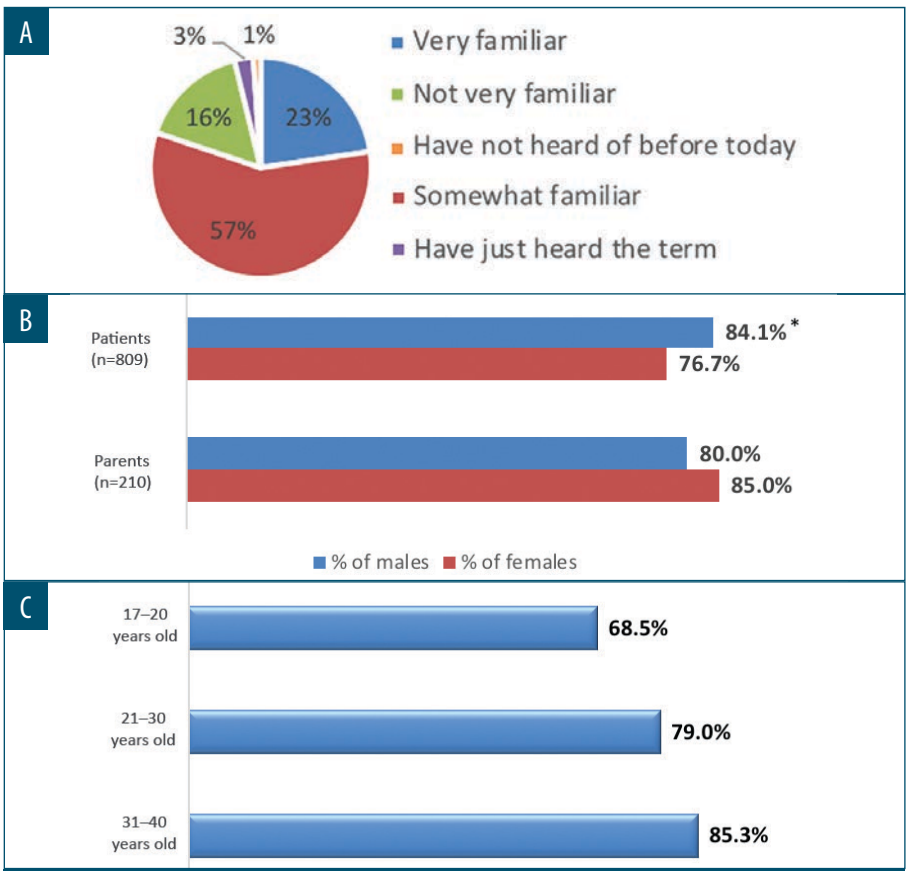

FIGURE 2. Respondent self-reported familiarity with antibiotic resistance (95% CI)—A) Familiarity with antibiotic resistance, all respondents (N=1,019); B) Patients vs. parents and male vs. female reporting "Very Familiar" or "Somewhat Familiar" with antibiotic resistance; C) Patients reporting "Very Familiar" or "Somewhat Familiar with antibiotic resistance by age (n=809)

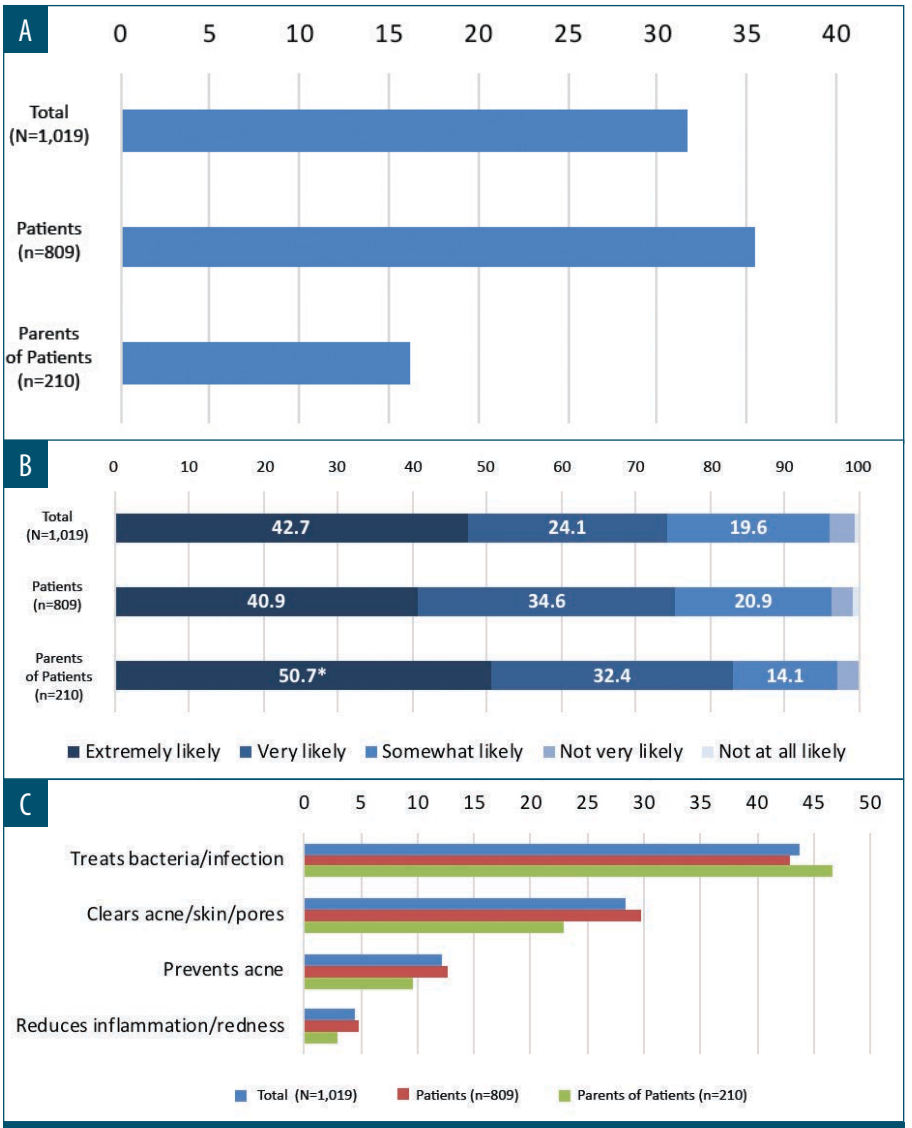

FIGURE 3. Self-reported awareness of antibiotic-free prescription options and the role of antibiotics in acne treatment (95% CI)—A) Aware of antibiotic-free prescription options (percent of antibiotic-using respondents; B) Likelihood to use antibiotic-free prescription, if effective (percent of antibiotic-using respondents; C) Role antibiotics play in treating acne (percent of respondents in top 4 response categories)

were aware of antibiotic-free prescription options. There was less awareness of antibiotic-free treatment options among parents than among patients (16.2% vs. 35.4%, respectively; Figure 3A). Among this population, 76.9 percent (75.4% patients, 83.1% parents, significantly different at 95% CI) said they would be very or extremely likely to use an antibiotic-free prescription treatment for AV if they were aware of the existence of effective, antibiotic-free therapeutic options (Figure 3B).

In the open-ended response to "what specific role do antibiotics play in treating acne?", the greatest proportion of responses (43.7%) were associated with the role of antibiotics in the treatment of bacteria or infection (Figure 3C). In contrast, a minority of respondents (18.4%) indicated a belief that AV is an infectious disease, with this belief significantly more prevalent among patients than among parent respondents (19.9% vs. 12.9%, respectively, significant at 95% CI). An additional 17.2 percent of subjects indicated they were undecided concerning the infectiousness of AV.

Among antibiotic users, the primary reason reported for choosing this treatment option was that the respondents felt it would be more effective than antibiotic-free prescription treatment options (43%). Other top responses included treatment duration (23.9%) and a lack of awareness of antibiotic-free prescription treatment options (22.8%). Among subjects who were prescribed antibiotic-free treatments, the top reasons reported for the use of an antibiotic-free treatment option were: 1) "felt it would be just as/more effective than antibiotics" (43.3%); 2) "concerns about potential risk of antibiotic resistance" (26.9%); and 3) "relative ease of treatment/application" (26.5%).

Emotional impact of acne. The majority of respondents reported that acne had an emotional impact on themselves or their children (Figure 4A), with 54.1 percent of respondents giving the impact a score of eight points or more on a 10-point scale, where 10="affects me greatly" and 1="does not affect me." A greater proportion of women reported that AV had a major emotional impact in that 60.3 percent of women versus 43.0 percent of men ranked emotional impact with a score of 8 or higher (Figure 4B). Overall, 43.5 percent of those surveyed agreed with the statement, "I care more about the emotional impact of my acne today than about the potential long-term impact of antibiotic resistance." When compared to parents, a greater percentage of patients with AV (46.7% vs. 31.0%) somewhat or completely agreed with this statement (significant at 95% CI). The difference between the two groups was driven by a low proportion of female parents displaying agreement (25.0%). A significantly greater proportion of patients, both male and female, as well as male parents agreed that the emotional impact of AV outweighs the risk of antibiotic resistance (significant at 95% CI). Of all parents surveyed, 65.7 percent reported that they had suffered from AV as a child or young adult. Of these, 47.8 percent ranked the emotional impact of AV as 8 or higher on a 10-point scale.

Conversations with dermatologists about antibiotic resistance related to acne. Of all respondents surveyed, only 35.3 percent had discussed the possible risks of antibiotic use as part of their AV treatment during recent conversations with their healthcare provider. These discussions were most often initiated by the doctor (65.6% of all reported discussions). Patients were more likely to report having discussed antibiotic risks with their doctor

than parents were (Figure 5), and male patients were significantly more likely to report these discussions than female patients (46.9% vs. 31.6%, respectively, significant at 95% CI). Few antibiotic users (including those unsure whether they had been prescribed an antibiotic) reported having discussed antibiotic-free AV treatment options with their prescriber (27.7%). Discussions concerning antibiotic-free treatment options were significantly more likely to occur among patients than parents (Figure 5; significant at 95% CI) and significantly more likely to occur among male patients than female patients (42.6% vs. 23.8%, respectively, significant at 95% CI).

Risks and actions related to antibiotic resistance. More than half of respondents (61.5%) reported that they had heard the term *superbug*, with 56 percent of all respondents reporting that they were aware of the risk and impact of superbugs. Parents were significantly more likely to report an awareness of superbugs compared to patients (72.9% vs. 58.6%, respectively, significant at 95% CI). A slightly higher percentage of female patients reported an awareness of superbugs compared to male patients (60.7% vs. 54.5%, respectively). The percentages of respondents who stated they were aware of specific health risks and costs (aided response question) associated with superbugs are presented in Table 3. Significant differences between the proportion of male and female patients and between patients and parents who correctly identified superbug-related risks were observed (significant at 95% CI). The respondents perceived a myriad of contributing factors to the propagation of superbugs, with overprescribing or unnecessary prescribing of antibiotics among the most commonly selected reasons for superbugs. In general, parents were more aware of causal factors than were current patients with AV (Table 4). A significantly greater percentage of female respondents were aware of causal factors related to antibiotic resistance compared to male respondents, including overprescribing of antibiotics, unnecessary prescribing of antibiotics, and not taking the complete course or duration of any prescribed antibiotic (significant at 95% CI). A significantly greater percentage of male respondents identified poor hygiene as a contributing factor leading to the propagation of superbugs (significant at 95% CI), compared to female respondents.

Subject agreement with a number of potential actions targeting antibiotic resistance was collected. The greatest proportion (>90%) of subjects agreed that doctors and other healthcare professionals should educate patients on antibiotic use and resistance (Figure 6). Parents were more likely than patients to agree with the proposed actions around antibiotic use, and female patients were more likely than male patients to agree with the proposed actions (significant at 95% CI; Table 5).

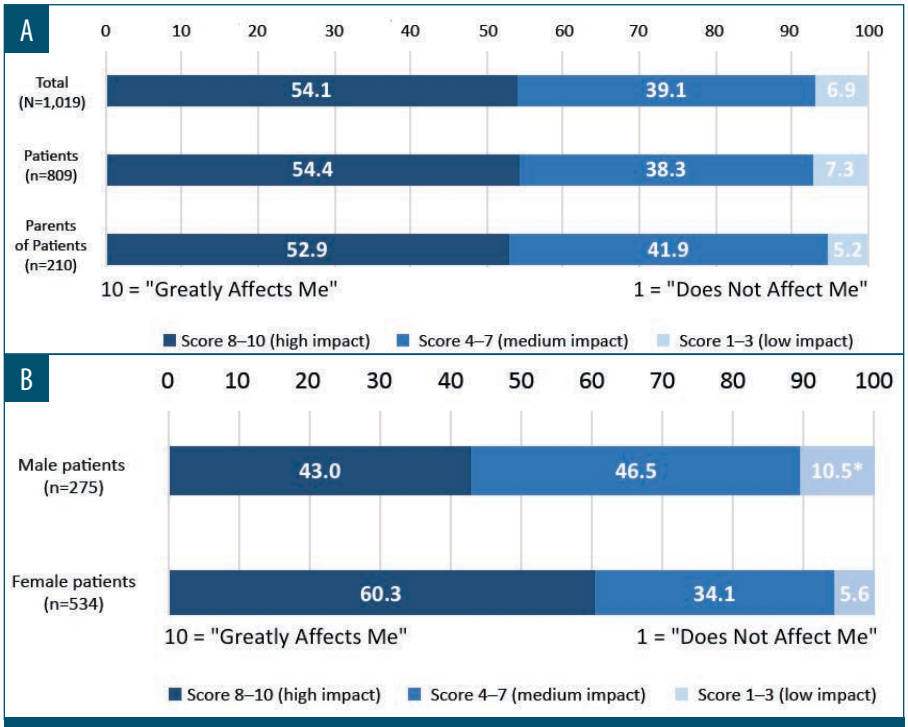

FIGURE 4. Self-reported emotional impact of acne, based on a scale of 1–10, where 1="does not affect me" and 10="greatly affects me"—A) Total respondents, % (N=1,019); B) Patient respondents, % (n=809)

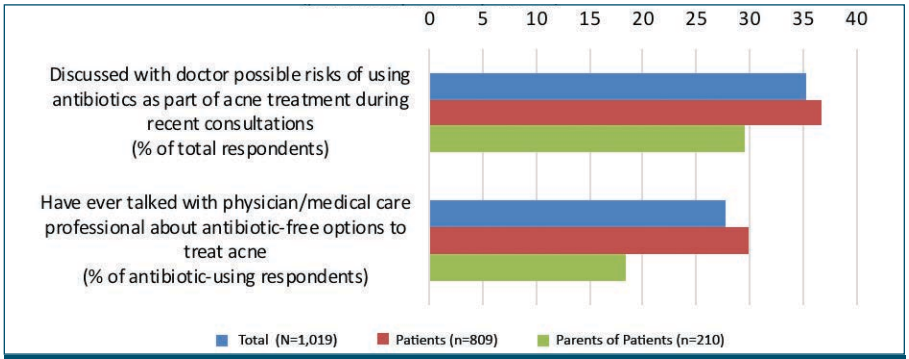

FIGURE 5. Reported conversations about antibiotic acne treatments, total respondents, % (N=1,019) (95% confidence interval)

DISCUSSION

This study reports the results of a survey of adults with AV and the parents of adolescents with AV. The survey assessed attitudes toward and awareness of antibiotic resistance and antibiotic use in AV. According to the results of this survey, adult patients with AV and parents of children/adolescents with AV have a basic grasp of antibiotic resistance, yet they underestimate many of the potential associated risks. Increased awareness was associated with increasing age within the surveyed population. Therefore, it might be important to focus on increasing awareness among younger patients with AV and to spend more time discussing the potential resistance-related risks of antibiotics with this population. Regarding the relative risk of antibiotic resistance, survey respondents

TABLE 3. Identification of risks/impacts of superbugs among respondents who reported an awareness of the risk of superbugs (N=1,019)

RISK OF SUPERBUGS	PATIENTS, % (n=809)			PARENTS, % (N=210)		
	TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE
Antibiotics will not work when I really need them	79.5	73.0	82.9*	91.3*	84.0	93.1
Risk of causing more serious illnesses/infections	80.9	73.0	84.9*	84.3	84.0	84.3
I or a loved one could be at risk for a hard-to-treat infection	71.6	58.6	78.4*	84.3*	80.0	85.3
Risk of death	70.0	65.1	72.6	83.5*	80.0	84.3
Medications and foods that I consume will become more expensive and harder to find	25.9	32.2*	22.6	22.0	32.0	19.6

*Significantly higher than the other group at the 95% CI

TABLE 4. Perceived causes of superbugs (aided response)

PERCEIVED CAUSES OF SUPERBUGS	TOTAL, % (N=1,019)	PATIENTS, % (n=809)	PARENTS OF PATIENTS, % (n=210)
Overprescribing of antibiotics	56.7	54.5	65.2*
Unnecessary prescribing of antibiotics	47.1	45.4	53.8*
Inappropriate infection-control procedures in hospitals and medical facilities	35.1	35.0	35.7
Not taking the complete course or duration of any prescribed antibiotic	33.6	31.9	40.0*
Poor hygiene	26.0	27.9*	18.6
Overuse of hand sanitizers	24.7	25.1	23.3
Other	0.5	0.4	1.0
Don't know	15.9	16.1	15.2

*Significantly higher than the other group at the 95% confidence level

perceived the use of oral antibiotics as a greater risk than the use of topical agents. Only a minority of respondents were aware of healthcare cost-related risks associated with superbugs, so education around the potential economic burden of superbugs (Table 3) is an area of opportunity.

The high emotional impact of AV increases the importance of efficacy in treatment decisions; however, consumers in this survey were clearly found to be open to or even prefer antibiotic-free options if the antibiotic-free treatment is effective. The results of this study demonstrate that patients with AV and parents of younger patients with AV feel that more should be done to combat antibiotic resistance, with most respondents placing the onus on healthcare professionals to educate patients on the topic. Antibiotics are a very important part of the AV therapeutic armamentarium. However, it is important that clinicians educate patients on antibiotic use and risks and incorporate exit plans when treating disorders such as AV when antibiotic therapy is prescribed.

Education surrounding antibiotic use: what more needs to be done?

Dermatological disorders, including AV and rosacea, frequently have a powerful psychosocial impact. Psychosocial consequences and negative changes in emotional and psychological health and well-being have been widely reported in the literature.[39,50–54] Furthermore, patients with AV can also develop scars, post-inflammatory hyperpigmentation, and erythema. These sequelae can persist for months or years after the active AV lesion that triggered them has resolved. In the present study, more than 70 percent of respondents reported that AV had a high emotional impact. A greater proportion of women than men reported that the disease had a high emotional impact. However, this patient population was also more likely to agree with statements of action regarding antibiotic resistance. Therefore, despite the need and desire for efficacious treatments for AV, survey respondents indicated that they would like more information about antibiotic-free treatment options and agreed that more should be done to raise awareness of issues related to antibiotic resistance.

Nearly 90 percent of those surveyed agreed that antibiotic prescriptions should be clearly labeled with information on the risks of antibiotic resistance. Additionally, more than 80 percent of subjects agreed that government agencies should do more to raise awareness about antibiotic resistance. The CDC has taken up this call through their "Get Smart about Antibiotics Week" initiative. This annual event aims to increase awareness and education concerning antibiotic use and antibiotic resistance. Similar programs are in place throughout the industrialized world.

Nearly all respondents surveyed agreed that healthcare professionals should be involved in efforts to educate patients about antibiotic resistance, and respondents ranked actions by healthcare professionals as being the most effective. This indicates that there is an opportunity to improve the existing dialogue between clinicians, their staff, patients with AV, and parents of patients that are minors. Notably, the results of the survey indicated a need for improved patient knowledge regarding the specific risks of antibiotic resistance, particularly healthcare cost-associated risks, and knowledge of antibiotic-free treatment options. Because the duration of antibiotic exposure is a critical factor in the propagation of antibiotic resistance, clinicians should be particularly mindful of educating patients with disorders that often require long-term treatment, such as AV. The World Health Organization has recommended that clinicians only prescribe antibiotics when

they are truly needed, utilizing an appropriate agent in the correct dose and for the correct duration of therapy.[14] The latter is not always clearly defined for adequate treatment of AV; however, attempts to limit prolonged oral antibiotic use are recommended.[10,14] This warrants an exit plan that incorporates topical therapy for long-term control of AV or transition to oral isotretinoin therapy when indicated. An open dialogue between clinicians and/or their staff and patients about the necessity for and alternatives to antibiotic therapies is consistent with the recommendation to limit oral antibiotic prescribing.

Antibiotic-free treatment options

Approximately 95 percent of patients and parents surveyed in this study did not think that AV could only be treated with antibiotics, and the majority responded that they would prefer to use an effective, antibiotic-free prescription treatment. Despite this, the awareness of antibiotic-free prescription AV treatments among antibiotic users was quite low. There are a number of effective, safe, antibiotic-free AV treatment options available to patients, and patient education on antibiotic-free treatment options is one avenue for expanding public knowledge and preventing the threat of increasing antibiotic resistance. Antibiotic-free AV treatment options are presented in Table 6.

Benzoyl peroxide. In terms of bactericidal action, benzoyl peroxide (BP) provides potent antimicrobial action with no known potential for inducing bacterial resistance. BP is effective at relatively low concentrations, even in the presence of sebum.[9,55–58] BP also has keratolytic properties, has been shown to reduce comedones in patients with AV , and might contribute indirectly to anti-inflammatory activity, which can also be beneficial in AV treatment.[57,59,60] Due to strong bactericidal action and a lack of resistance induction, some authors have recommended that BP be added to any antibiotic treatment for AV.[9,10,32] However, topical BP will not prevent alterations in systemic flora, including the development of antibiotic-resistant bacteria and changes in the GI tract microbiome, resulting from the use of oral antibiotics. Fixed-dose combination products containing BP and either clindamycin or erythromycin have been approved for the treatment of AV.[61–64] It should be noted that *C. acnes* resistance to erythromycin is widespread, resistance to clindamycin has been observed, and cross-resistance among *C. acnes* strains to both antibiotics is common.[65–68] The incorporation of BP in combination with a topical antibiotic (used as a fixed combination product), such as erythromycin, has been shown to prevent the emergence and proliferation of antibiotic-resistant *C. acnes* strains, at least at sites where the BP is applied.[9,69,70]

FIGURE 6. Respondent agreement with proposed actions on antibiotic resistance, % (N=1,019)

Retinoids. Retinoids are an effective alternative to antibiotic treatment for AV and are recommended for both initial and maintenance of AV by the American Academy of Dermatology and the Global Alliance to Improve Outcomes in Acne.[9,10,32] Retinoids have keratolytic and anti-comedogenic properties, exhibit direct anti-inflammatory activity via downregulation of Toll-like receptor-2 (TLR-2, and might contribute to dermal matrix integrity and acne scar mitigation through the stimulation of collagen production.[13,14,59,71,72] Fixed-dose combinations of the retinoid adapalene with BP are also available and are an effective antibiotic-free topical option for AV treatment.[9]

Dapsone. Topical dapsone might serve as an antibiotic-free option for AV, though whether currently marketed topical dapsone

TABLE 5. Respondent agreement with actions on antibiotic resistance (by subpopulation)

RESPONDENT AGREEMENT (AGREE COMPLETELY/SOMEWHAT AGREE)	PATIENTS, % (N=809)			PARENTS OF PATIENTS, % (N=210)		
	TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE
Doctors should ensure that patients are educated about how much and for how long antibiotics should be used	90.9	85.6	93.6*	96.2*	92.0	97.5
Health care professionals should do more to educate patients on antibiotic resistance	91.1	89.5	91.9	95.2*	94.0	95.6
Antibiotic prescriptions should be clearly labeled with information on the risks of antibiotic resistance	89.1	83.8	91.9*	92.9	94.0	92.5
More people should talk to their doctor about concerns with antibiotic resistance	88.5	84.8	90.4*	92.4	86.0	94.4
Pharmacists should do more to inform patients about the risks of antibiotics	85.9	84.5	86.7	86.7	90.0	85.6
Government agencies should do more to raise awareness about antibiotic resistance	83.2	80.5	84.6	87.1	84.0	88.1
My insurance company should reimburse antibiotic-free treatments for conditions, such as acne, so that I have options	79.7	77.3	81.0	86.2*	82.0	87.5
There should be a law requiring doctors to inform patients about the risks of antibiotic resistance when prescribing antibiotics	80.3	79.4	80.8	74.3	68.0	76.3
The FDA should require that antibiotics only be used when there are no antibiotic-free treatments available	70.7	73.3	69.4	70.5	68.0	71.3

*Significantly higher than the other group at the 95% confidence level (total sufferers vs. total parents or male vs. female)

formulations exhibit antibiotic activity and/or affects the cutaneous flora remains unknown. *In vitro*, dapsone demonstrates antimicrobial activity against a wide range of gram-positive bacteria, with several species (including *S. aureus*, *Staphylococcus epidermidis* [*S. epidermidis*], *Streptococcus pyogenes* [*S. pyogenes*], and *Streptococcus agalactiae* [*S. agalactiae*]) exhibiting a minimum inhibitory concentration (MIC)50 of 128µg/mL or less.[73] A topical dapsone 2% nanoemulsion has shown very high (11,963,837.34µg/cm^2) local skin concentrations, and therefore, might affect many commensal and pathogenic bacteria.[73,74]

CONCLUSION

Our survey results suggest that the majority of patients with AV and parents of young patients with AV are aware of and concerned about the impact of antibiotic resistance. Adult patients with AV and parents of younger patients with AV have a general understanding of the risks associated with antibiotic resistance and many of the potential causes of antibiotic resistance; however, they underestimate the role of topical treatments in the development of antibiotic resistance. Most of the respondents were not aware of antibiotic-free treatment options, but the vast majority were open to using an effective, antibiotic-free treatment for AV on themselves or their children. This study highlights an existing desire among patients with AV for more information from their clinicians about antibiotic resistance risk and alternative therapies for AV.

A full understanding of the mechanisms of action of antibiotics in AV is not known; however, the reduction of *C. acnes* appears to be one factor that correlates with clinical improvement, and its increasing resistance to antibiotics has been associated with reduced efficacy of antibiotic therapy for AV.[75–77] Anti-inflammatory properties of some antibiotics (e.g., tetracyclines, macrolides) might also contribute to their therapeutic effects for AV.[36,75,78] Moreover, while antibiotic resistance can develop quickly and is widespread, both oral and topical antibiotics are often prescribed for extended periods. This suggests that the anti-inflammatory contribution of antibiotics to AV treatment is significant.[4,79–82] Subantibiotic dosing of oral antibiotics or combining topical antibiotics with BP are two potential approaches to mitigating the risk of antibiotic resistance while harnessing the anti-inflammatory effects of antibiotics.[9,10,83,84] Antibiotics are widely prescribed in dermatology; therefore, judicious use of antibiotics in the treatment of noninfectious dermatological diseases (such as AV and rosacea) and increased education of dermatology patients have the potential for great impact in the stewardship of antibiotic therapies.

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TABLE 6. Antibiotic-free and subantimicrobial AV treatment options

CATEGORY	THERAPY	APPROVED FOR AV?	AAD RECOMMENDATION STRENGTH	AAD ACNE SEVERITY RECOMMENDATION		
				MILD	MODERATE	SEVERE
Benzoyl Peroxide	Wash and leave-on products in varying concentrations	Yes (OTC, monograph)	A	X	X	X
Topical retinoids	Adapalene, tazerotene, tretinoin	Yes (adapalene 0.1%, also OTC)	A	X	X	X
Combination retinoid/benzoyl peroxide	Adapalene 0.3%/BPO 2.5% gel; adapalene 0.1%/BPO 2.5% gel	Yes	A	X	X	X
Dapsone	5%, 7.5% gel	Yes	A	X		
Oral contraceptives (combined estrogen/progestin)	Various formulations, use in women only	Approved for female AV: ethinyl estradiol/ norgestimate; ethinyl estradiol/ norethindrone acetate/ferrous fumarate; ethinyl estradiol/ drospirenone; ethinyl estradiol/ drospirenone/ levomefolate	A		X	X
Azelaic acid	20% cream	Yes (20% cream only; other formulations exist)	A			
Oral isotretinoin		Yes	A		X	X
Spironolactone	Typical doses range from 50–200mg	Yes	A		X	X
Salycylic acid		Yes (OTC, monograph)	B			
Oral corticosteroids			B			
Chemical peels	Glycolic acid, salicylic acid peels		B			
Flutamide		No	C			
Intralesional steroids			C			
Subantibiotic dose doxycycline	40mg modified-release doxycycline monohydrate once daily; 20mg doxycyclate hyclate twice daily	No	NA			
Niacinamide	2%–4% gel	No (OTC)	NA			
Laser/light therapy	Blue and red light devices, infrared, pulsed-dye laser, photodynamic therapy, intense pulsed light, photpneumatic therapy, particle assisted photothermolysis	Some (infrared, photopneumatic therapy)	NA			

AAD: American Academy of Dermatology; OTC: over-the-counter; BPO: benzoyl peroxide
Strength of recommendation is as follows: A: Recommendation based on consistent and good-quality, patient-oriented evidence; B: Recommendation based on inconsistent or limited-quality, patient-oriented evidence; C: Recommendation based on consensus, opinion, case studies, or clinical evidence

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