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Jelena Lewis
Chapman University, jelewis@chapman.edu

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Comments

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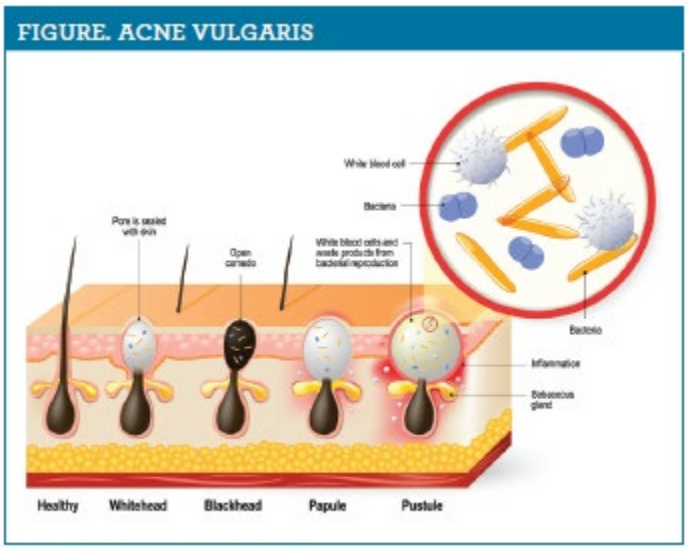
Jelena Lewis, PharmD

About 50 million people in the Unites States have acne vulgaris (AV) (figure[1]), a common inflammatory skin disease that predominantly affects adolescents and young adults. Although it can occur in any age group, AV affects about 85% of teenagers.[1,2] The prevalence of acne in adult women is about 12%.[3] Although acne is not associated with mortality, it does pose a physical and psychological burden to the patient, which may result in depression, negative body image, stress, and anxiety. The direct cost of the disease is estimated to exceed $3 billion per year.[2] Therefore, it is imperative that clinicians are familiar with the management of AV, which consists of topical therapies, systemic antibiotics, hormonal agents, and isotretinoin.[4] A treatment algorithm for the management of AV in adolescents and young adults is outlined in the table[4].



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TOPICAL THERAPIES

Topical therapies used for acne treatment may be OTC or prescription products. Commonly used topical acne products include benzoyl peroxide (BP), either as monotherapy or in combination; antibiotics and retinoids, either as monotherapy or in combination; salicylic acid; azelaic acid; and sulfone agents.[4]

BP may be used as monotherapy or in combination with topical erythromycin or clindamycin for treatment of mild acne[4]; BP may also be used in conjunction with a topical retinoid or systemic antibiotic therapy for treatment of moderate to severe acne.[4] BP is an antibacterial agent with low likelihood of resistance. Formulations of topical BP include washes, foams, creams, and gels, used in both leave-on or wash-off agents.[4] Topical BP products are available in the strengths of 2.5% to 10% and results may be seen in as little as 5 days.[4,5] Adverse effects (AEs) include concentration-dependent irritation and contact allergy which are uncommon. Longer skin contact times and certain formulations may provide better results. Lower BP concentrations and wash-off agents may be preferred in patients with sensitive skin. BP can safely be used in the management of preadolescent acne in children. Patients should be made aware that BP may stain or bleach fabrics.[4]

Most patients with acne will need combination therapy. The addition of BP to antibiotic therapy enhances results, and reduces development of resistant bacterial strains. Monotherapy with topical antibiotics is not recommended due to increased risk for antibiotic resistance. Clindamycin 1% and erythromycin 2% are topical antibiotics available for the treatment of acne and are available as fixed-combination agents with BP. Topical clindamycin is preferred over topical erythromycin as some bacteria are resistant to erythromycin. Topical antibiotics are well tolerated and treatment is associated with a low risk of AEs (eg, diarrhea).[4]

Retinoids are an important first-line topical therapy for comedonal acne; however, retinoids increase the efficacy and acne-clearing benefits when used with other topical or oral agents in combination regimens. Retinoids function to resolve the primary acne lesion, as well as inhibit the formation of new comedones, and they have anti-inflammatory properties. Taken together with other topical or oral agents, retinoid treatment allows for extended acne clearance in the maintenance phase after cessation of oral therapy.[4] Tretinoin, adapalene, and tazarotene are topical retinoids and vitamin A derivatives used in the treatment of acne. Of the retinoid combination products available for the topical treatment of acne, 2 topical gel products are formulated with a fixed combination of retinoid and antibiotic agents (clindamycin phosphate 1.2%/tretinoin 0.025%) and 2 topical gel products are formulated with a fixed combination of retinoid and BP (adapalene 0.1%/BP 2.5%).[4,6-8] Most retinoids are approved by the FDA for patients ≥12 years of age with the exception of tretinoin 0.05% micronized tretinoin gel, which is approved for patients ≥10 years of age, and adapalene 0.1%/BP 2.5%, which is approved for patients ≥9 years of age.[4] Patients treated with retinoids may experience AEs including dryness, peeling, irritation, and erythema.[4,9] Patients using both tretinoin and BP should be counseled about applying these 2 products at different times, as tretinoin may be deactivated by BP. Tretinoin microsphere formulation, adapalene, and tazarotene do not have these restrictions. Patients using retinoids should also be counseled to wear sunscreen daily, as these agents have an increased risk of photosensitivity. Prior to initiating treatment with tazarotene, a negative pregnancy test should be ensured and patients should be counseled regarding pregnancy risks, as this medication is classified as pregnancy category X. Tretinoin and adapalene are classified as pregnancy category C.[4] There are limited data as to which retinoid is most effective. Therefore, which product to use may simply be patient or physician preference.

Azelaic acid 20% is a mildly effective agent and has benefits in patients with sensitive skin. It is useful as an adjunctive agent and can be recommended in the treatment of post-inflammatory dyspigmentation.[4]

Dapsone 5% gel is a sulfone agent used twice daily and it has modest to moderate efficacy. Dapsone is believed to provide benefit as an anti-inflammatory agent; however, treatment has demonstrated increased benefits in women compared with effects in men and adolescents.[4,10,11] When used with BP, dapsone may cause orange-brown coloration of the skin, which may be washed off.[4] Patients should be counseled regarding this occurrence. Dapsone is indicated for patients ≥12 years old and it does not necessitate glucose-6-phosphate dehydrogenase testing prior to the start of the medication.[4]

The topical therapies salicylic acid, sulfur, resorcinol, aluminum chloride, topical zinc alone,

sodium sulfacetamide, and topical niacinamide all have limited data regarding efficacy for the treatment of AV.[4]

TABLE. TREATMENT ALGORITHM FOR THE MANAGEMENT OF ACNE VULGARIS IN ADOLESCENTS AND YOUNG ADULTS[4]

	Mild	Moderate	Severe
First-line treatment	Benzoyl peroxide (BP) OR topical retinoid OR topical combination therapy[a] (BP + antibiotic) OR (retinoid + BP) OR (retinoid + BP + antibiotic)	Topical combination therapy[a] (BP + antibiotic) OR (retinoid + BP) OR (retinoid + BP + antibiotic) OR (oral antibiotic + topical retinoid + BP) OR (oral antibiotic + topical retinoid + BP + topical antibiotic)	Oral antibiotic plus topical combination therapy[a] (BP + antibiotic) OR (retinoid + BP) OR (retinoid + BP + antibiotic) OR Oral isotretinoin
Alternative treatment	Add topical retinoid or BP (if not already applied) OR Consider alternate retinoid OR Consider topical dapsone	Consider alternate combination therapy OR Consider change in oral antibiotic OR Add combined oral contraceptive or oral spironolactone (females) OR Consider oral isotretinoin	Consider change in oral antibiotic OR Add combined oral contraceptive or oral spironolactone (females) OR Consider oral isotretinoin

[a]May be prescribed as a fixed combination product or as a separate component.

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SYSTEMIC ANTIBIOTICS

Systemic antibiotics are used for moderate to severe inflammatory acne and should be used in combination with a topical retinoid or BP.[4,12-14] The tetracycline class of antibiotics is considered a first-line treatment for moderate to severe acne. Both doxycycline and minocycline have demonstrated increased efficacy compared with tetracycline in the treatment of moderate to severe acne; however, there are no differences in efficacy between the 2 systemic antibiotic treatments. Macrolide antibiotics such as erythromycin or azithromycin can also be used in the treatment of acne, but these agents are usually reserved for patients who cannot take tetracyclines (ie, children <8 years of age and pregnant women). Data are limited for the use of systemic antibiotics, other than tetracyclines and macrolides, for the treatment of acne.[4]

Patients may ask about the AEs of taking systemic antibiotics for acne. Severe AEs of systemic antibiotics in the treatment of acne are rare.[4] Photosensitivity is a major AE of tetracyclines. Gastrointestinal (GI) disturbances have also been reported. Fewer case reports of AEs have been reported for doxycycline than minocycline.[4,15] AEs associated with minocycline include dizziness and tinnitus, as well as pigment deposition of the teeth, mucous membranes, and skin.[4] Minocycline may also cause more serious AEs such as autoimmune disorders, drug-induced lupus, and other hypersensitivity reactions, while the predominant serious AE for doxycycline is esophageal erosion.[15] Macrolides are also associated with GI disturbances, and this is higher with erythromycin than azithromycin. This class of antibiotics may cause cardiac conduction abnormalities, and azithromycin has also been associated with cutaneous hypersensitivity reaction. Although some patients may need prolonged therapy with systemic antibiotics for the treatment of AV, limiting use of these agents to 3 months is preferred in order to avoid antibiotic

resistance. Systemic antibiotics should be administered concomitantly with either a topical therapy with BP or a retinoid; this topical treatment can continue for maintenance after systemic antibiotic therapy has been completed.[4]

HORMONAL AGENTS

Ethinyl estradiol/norgestimate, ethinyl estradiol/norethindrone acetate/ferrous fumarate, ethinyl estradiol/drospirenone, and ethinyl estradiol/drospirenone/levomefolate are the 4 combination oral contraceptive pills (COCs) approved by the FDA for the treatment of AV in women who also desire contraception. All 4 of these medications are equally efficacious when used for the treatment of AV and may be used alone or in combination with other treatments. Venous thromboembolic events, myocardial infarction (MI), ischemic and hemorrhagic stroke, breast cancer, and cervical cancer are associated with COC use. MI risk is strongly associated with cigarette smoking, diabetes mellitus, and hypertension. Cigarette smoking and hypertension contribute to increased risk of stroke, as do higher doses of ethinyl estradiol and being older than 35 years of age. Furthermore, due to concern regarding COC use in younger adolescent populations given the effects of low estrogen on bone mass, the use of COC for acne should be avoided unless the patient is at least 14 years of age and started menses more than 2 years prior to treatment. COCs used for the treatment of AV are approved for female patients desiring contraception who are either ≥14 or ≥15 years of age. Patients should also be counseled that the benefits of COC therapy will not be seen immediately and that the visible effects may take several months.[4]

Spironolactone is not FDA-approved for the treatment of AV. However, the guidelines produced by the American Academy of Dermatology (AAD) for the care and management of acne vulgaris support the use of spironolactone in the management of acne in select women. Spironolactone has a black box warning that it has been shown to be a tumorigen in chronic toxicity studies in rats; because of this, off-label use of spironolactone should be avoided. One report documented carcinogenicity associated with spironolactone treatment in 5 hospitalized patients with breast cancer; however, additional retrospective studies have shown no association between spironolactone use and breast cancer. Spironolactone may be used safely with drospirenone-containing COCs. Serum potassium monitoring is recommended for high-risk patients who are older or taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, or digoxin.[4] Patients taking this medication should be counseled to avoid potassium-rich foods, such as low-sodium processed foods and coconut water.[4,16]

ISOTRETINOIN

Oral isotretinoin has been used in the United States for more than 30 years and is approved by the FDA for the treatment of severely recalcitrant AV. AAD guidelines of care for the management of AV also support the use of oral isotretinoin for use in moderate AV that is treatment-resistant or quick-relapsing, or in patients who have significant scarring or psychosocial issues due to AV. Patients taking isotretinoin should be counseled to take this medication with food. Isotretinoin treatment is associated with AEs including inflammatory bowel disease (IBD), cardiovascular risk factors, depression or other mood changes, bone demineralization, concerns regarding scarring with procedures such as dermabrasion or laser resurfacing, and Staphylococcus aureus colonization which may increase the risk for skin

infections.[4] Although the risk for these AEs is low, patients should be educated regarding the potential risks for these events. The AAD states that the evidence is insufficient to prove either an association or causal relationship between isotretinoin use and IBD. The AAD also states that an evidence-based causal relationship between isotretinoin use and depression/anxiety symptoms has not been established.[17] Liver function tests and lipid panel should be routinely monitored while on isotretinoin therapy. Complete blood cell counts are not necessary.[4] Isotretinoin is a teratogen and patients must be counseled regarding this. All patients (not just women), prescribers, pharmacies, and manufacturers must register with the iPLEDGE program, which was designed to prevent fetal exposure to isotretinoin. Despite this, fetal exposure has not significantly decreased since the implementation of iPLEDGE, and about 150 isotretinoin-exposed pregnancies still occur annually in the United States.[18,19] Therefore, pharmacists must be diligent about counseling patients regarding either abstinence or the importance of adherence to 2 contraceptive methods as per iPLEDGE requirements.[19]

OTHER THERAPIES

Other therapies for the treatment of acne include glycolic acid peels, salicylic acid peels, and pulsed dye laser treatments; however, there is little evidence to support the recommendation of these procedures. Safety and efficacy have not been established for complementary and alternative therapies for the treatment of AV. Currently, there is no “acne diet”; however, some data show that a diet with a high glycemic index and intake of dairy products may predispose patients to acne.[4]

CONCLUSION

Many available agents are used for the management of AV. These agents may cause AEs or require routine lab monitoring in certain patients. Pharmacists should ensure that patients taking these medications are counseled regarding potential AEs, and they should recommend routine laboratory monitoring to patients and physicians as deemed appropriate.

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Jelena Lewis, PharmD, is an assistant professor of pharmacy practice at Chapman University School of Pharmacy, Irvine, California, and faculty in residence at St. Jude Heritage Medical Group, Fullerton, California.