

CLINICAL UPDATE ON ACNE*

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ABSTRACT

Acne is the most common skin condition in the United States, affecting nearly all adolescents but also a large number of adults. Several pathogenic processes contribute to the formation of acne. Hormonal stimulation of the sebaceous glands causes plugging of these glands by keratinous debris and sebum, resulting in the formation of microcomedones. Colonization of microcomedones by bacteria results in inflammation and the formation of papules, pustules, cysts, and ultimately scarring. Medications are available to target several points in the pathogenic processes that cause acne. Topical agents include a number of formulations of benzoyl peroxide, antibiotics, and products that combine benzoyl peroxide and a topical antibiotic. Combining a topical antibiotic with benzoyl peroxide results in rapid reduction of bacteria at the skin surface, reduces the development of antibiotic-resistant bacteria, produces better efficacy, and improves treatment adherence. Topical retinoids produce comedolytic and anti-inflammatory effects, and are available in several formulations. Some products also

combine topical retinoids with a topical antibiotic. Systemic options include oral antibiotics, oral contraceptives, the antiandrogen spironolactone, and the oral retinoid isotretinoin. Light therapy may improve acne or reduce scarring, but is primarily used by dermatologists who also have a strong focus in cosmesis. Combining 2 or more medications that target different points in the pathogenesis of acne makes it possible to step up treatment intensity for patients with more severe or persistent acne. Even severe acne may be effectively treated in the family practice setting using a combination of various approaches. Referral to a dermatologist may be considered for patients who have severe, potentially scarring acne or those who have not responded adequately to treatment.

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Acne is the most common skin condition in the United States, affecting an estimated 40 to 50 million people. Although acne affects virtually all adolescents, it should also be noted that 40% to 55% of adults older than the age of 25 years have persistent acne.¹ Acne is associated with considerable psychosocial impact, and may contribute to social withdrawal, poor body image, decreased self-esteem, depression, frustration, anger, embarrassment, preoccupation with appearance, and even employment difficulties.^{2,3} In many cases, acne is accompanied by significant postinflammatory hyperpigmentation and permanent scarring. Despite the considerable preva-

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lence and burden of acne, most patients attempt to self-treat it using nonprescription medications, cleansers, astringents, facial pads, and similar methods. Only approximately 33% of patients seek help from a healthcare professional for their acne and obtain a prescription medication.⁴ The low proportion of patients with acne who seek medical attention likely reflects the still common but mistaken belief that acne is caused by poor skin hygiene, and that it may be ameliorated by more frequent washing of the face.

Acne is caused by the interaction of several pathogenic processes that occur both at and below the skin surface. Beginning at approximately age 9 to 10 years, increased hormonal stimulation of the sebaceous gland (primarily by androgens) results in abnormal keratinization, desquamation, and oil production.⁵ The accumulation of keratinous debris and sebum cause the follicle to become plugged and distended, which results in the clinical appearance of a microcomedone at the skin surface. The colonization of the microcomedone by the bacterium *Propionibacterium acnes* triggers an inflammatory cascade that results in the characteristic papule or pustule of acne. Progression of inflammation may lead to the formation of skin cysts, and ultimately to scarring. These pathophysiological mechanisms suggest a number of specific treatment goals to reduce acne lesions and prevent scarring and postinflammatory hyperpigmentation. These goals include normalization of keratinization, lysis of comedones, suppression of the overproduction of sebum, and elimination of bacteria, all of which play an important role in the control of inflammation. As described later in this article, acne medications are available that target several different stages of acne pathogenesis. Educating patients about the pathogenesis of acne and how medications impact different stages of acne pathogenesis is essential in improving patient adherence to treatment.

Representative acne lesions are shown in Figure 1. Noninflammatory acne, consisting primarily of open or closed comedones, is shown in Panel A. The remaining panels illustrate inflammatory acne, including the appearance of papules, pustules, scarring, and the formation of nodules (larger lesions that may encompass more than 1 follicle). Conditions that are commonly mistaken for acne include keratosis pilaris and adenoma sebaceum. Keratosis pilaris is very common, and is characterized by monomorphic, slightly hyperkeratotic lesions with a sandpaper-like feel on

Figure 1. Acne Lesions

A. Early noninflammatory, comedonal acne



B. Inflammatory mixed comedonal and papulo-pustular acne



C. Inflammatory comedonal, papular, and early scarring acne



D. Cystic, nodular, inflammatory acne



EVIDENCE-BASED PRACTICE RECOMMENDATIONS

I. Practice Recommendation: The pathogenesis of acne is multifactorial, and includes hormonal, microbiological, and immunological mechanisms. Acne treatments should be combined to target as many pathogenic factors as possible. Topical antibiotics alone may increase the risk of antibiotic resistance. Patients who require topical antibiotic therapy should be treated with benzoyl peroxide in combination with erythromycin or clindamycin.

Name of AAFP-Approved Source: American Academy of Dermatology: Guidelines of Care for Acne Vulgaris Management.

Specific Web Site of Supporting Evidence from Approved Source: http://www.aad.org/pm/science/_docs/ClinicalResearch_Acne%20Vulgaris.pdf.

Strength of Evidence: A work group of experts in the management of acne, convened by the American Academy of Dermatology, performed an evidence-based review of the effectiveness of acne management strategies. This review identified 5 clinical studies (4 randomized, double-blind, vehicle-controlled studies and 1 randomized single-blind study) with a combined population of 1278 patients that have shown that combinations of benzoyl peroxide and a topical antibiotic reduce or eliminate antibiotic resistance with topical antibiotic therapy, and are more effective than either individual treatment alone (strength of recommendation, A).

II. Practice Recommendation: Many patients require systemic therapy to treat more severe acne. Systemic antibiotics should be used to treat moderate-to-severe acne or treatment-resistant forms of inflammatory acne.

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Strength of Evidence: The American Academy of Dermatology expert consensus panel also reviewed the use of systemic acne therapy. The panel concluded that systemic treatment with antibiotics is part of the standard of care for the patients with moderate-to-severe acne or treatment-resistant acne. The review identified 3 randomized, double-blind, vehicle-controlled clinical trials with a combined population of 515 patients supporting the use of tetracycline, and 3 randomized, double-blind, vehicle-controlled or active comparator-controlled clinical trials with a combined population of 258 patients supporting the use of macrolides (strength of recommendation, A).

palpation, which are often found on the outer arms and thighs. Keratosis pilaris lesions of the face often cluster primarily on the cheeks, and tend to spare the forehead. Adenoma sebaceum is rare, and typically presents in a center-facial pattern. These lesions tend to be deep-seated and tightly clustered. Eruptive vellus hair cysts may also be mistaken for acne, although they are more commonly seen on the chest.

ACNE THERAPY OPTIONS

Several topical and systemic medications are available for acne treatment.^{6,7} As shown in Figure 2, various treatment options that may be used concurrently for optimal control are available to target the different components of acne pathogenesis. Treatment usually begins with a topical agent. Benzoyl peroxide, which has antibacterial and anti-inflammatory properties, is available as a gel or wash. Additionally, topical antibiotics are available in several gel-based or cream-based formulations. Topical retinoids provide a comedolytic effect and are also anti-inflammatory. The principal systemic options include antibiotics, oral contraceptives, and retinoids. Other systemic treatments are sometimes used, including spironolactone, antiandrogens, and, rarely, oral or intralesional corticosteroids.

Several combination topical products that contain benzoyl peroxide are available; some products are available as a wash, which is particularly helpful for patients who cannot tolerate benzoyl peroxide on the skin for long periods, or who have widespread acne over a large body surface (eg, the chest or back). Many products combine benzoyl peroxide with a topical antibiotic, usually clindamycin. This approach is potentially advantageous for several reasons. These products target 2 or more different pathophysiological processes that can cause acne, and clinical studies have demonstrated that the combination of benzoyl peroxide and a topical antibiotic (eg, clindamycin or erythromycin) is more effective than either active ingredient alone.^{8,9} Clinical studies have demonstrated that combination products that contain benzoyl peroxide and a topical antibiotic are associated with a reduced risk of antibiotic resistance, which is one of the most important obstacles to current acne therapy. Topical application of a combination of benzoyl peroxide and clindamycin has been shown to reduce *P acnes* at the skin surface by 90% within 1 day, and to prevent the appearance of antibiotic-resistant bacte-

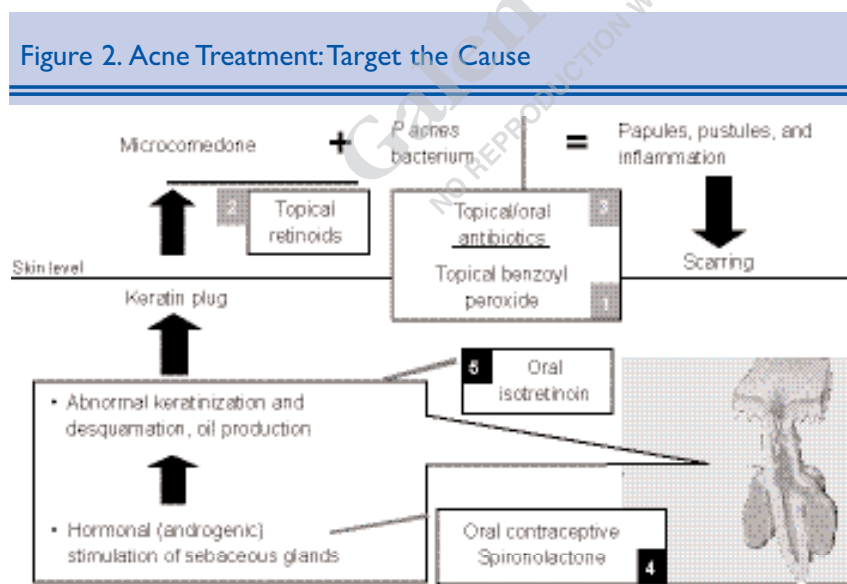
ria.¹⁰ In addition, a combination product is more convenient for patients than using 2 or more different therapies, which may help to improve treatment adherence.

Topical retinoids used for acne therapy contain 1 of 3 active ingredients, each of which is available in a variety of different formulations.¹¹ Tretinoin is available as a cream or gel, as a liquid, as a microsphere-based gel, and as a polymerized cream or gel, at concentrations from 0.01% to 0.1%. Adapalene is available as a cream, gel, solution, or pledgets, in concentrations of 0.1% to 0.3%. Tazarotene is available in cream or gel formulations in concentrations of 0.05% to 0.1%. A combination product containing topical clindamycin and tretinoin is also available.¹² A cream-based product is often beneficial for a patient with very sensitive skin. Regardless of the specific product chosen, all of the retinoid-containing topical treatments have the potential to produce skin irritation, dryness, and some degree of photosensitivity. These effects of treatment should be discussed with the patient before the product is prescribed. Patients should also understand that an initial period of adaptation to these medications may be required (a process referred to as retinization), but that skin irritation is expected to decrease after the first few

weeks of treatment. Topical retinoids may initially be applied every other day until the individual patient's skin has adapted to the medication.

Oral antibiotics are commonly used as first-line therapy for patients with more severe or inflammatory acne.^{6,13} Tetracycline and erythromycin are usually administered at doses of 250 to 500 mg twice daily; doxycycline and minocycline are usually administered at doses of 50 to 100 mg daily or twice daily.⁶ The use of tetracycline may be difficult for some patients to tolerate, as it must be taken on an empty stomach and may cause gastrointestinal side effects. Doxycycline may be a good alternative, although patients should be advised to take it with food and water to minimize gastrointestinal effects. Doxycycline and tetracycline are also associated with photosensitivity. Minocycline is also frequently used for acne therapy, but is generally not used as first-line therapy due to relatively high cost and as yet limited efficacy data from controlled clinical trials.^{7,14} Some patients experience headache or dizziness with minocycline, especially at the beginning of treatment. Patients should also be warned about the potential for pseudotumor cerebri, a condition that is characterized by increased intracranial pressure, presenting with severe headache, nausea, and visual disturbance, which is a rare side effect of all of the cycline-based antibiotics.¹⁵ If not recognized early, pseudotumor cerebri may cause permanent and severe visual loss.¹⁶ Another significant concern with oral antibiotics is the growing prevalence of antibiotic-resistant bacteria. Resistance to erythromycin is especially common, which is the principal reason why this agent is used infrequently in current dermatology practice. Erythromycin may be used for patients who are not candidates for tetracycline therapy either due to young age and associated concern for teeth discoloration or known allergy to cycline antibiotics.

The availability of a variety of acne therapies that target different pathogenic processes provides the opportunity to combine medications to gradually step up the intensity of therapy. Topical benzoyl peroxide may be sufficient for early, mild acne. A topical retinoid may



Several acne therapies are available to target the processes that contribute to acne pathogenesis, including *Propionibacterium acnes* activity (antibiotics and benzoyl peroxide), microcomedone formation (topical retinoids), hormonal stimulation of sebaceous glands (oral contraceptives and spironolactone), and keratinization, desquamation, and oil production (oral isotretinoin).

be added for comedonal involvement. The 2 topical agents may be applied at different times of the day (eg, benzoyl peroxide every morning, and topical retinoid every evening) or on alternate days to improve tolerability and adherence. Persistent inflammation may be addressed by the addition of a topical antibiotic, or a combination product that contains a topical antibiotic with benzoyl peroxide. For deep-seated lesions or widespread involvement of the back or chest, an oral antibiotic may be required to attain a deeper anti-inflammatory response.

Oral contraceptives may be helpful for female patients who do not respond sufficiently to these therapies, and are especially useful for patients who additionally experience perimenstrual acne flares or irregular or painful menses. Antiandrogens (eg, spironolactone) are also used for systemic therapy for some female patients with severe acne. A recent clinical study of women with severe papular or nodulocystic acne demonstrated that the combination of an oral contraceptive (30 µg ethinyl estradiol and 3 mg drospirenone) and spironolactone (100 mg daily) produced clearing or substantial improvement in 85% of patients.¹⁷ Only 7% of patients exhibited no improvement from baseline.

Some patients with severe acne benefit from oral isotretinoin. Isotretinoin produces a number of physiological effects that are especially helpful in acne therapy, including suppression of abnormal keratinization and desquamation, reduction of sebum levels, comedolysis, and antibacterial properties.¹⁸ Oral retinoid therapy has been shown to markedly improve severe acne. One clinical trial examined the effects of oral isotretinoin in 88 patients with severe acne, with follow-up for as long as 10 years after treatment. Improvement of at least 85% in acne severity from baseline was noted for 60% of patients after 4 months. After 10 years, 61% of patients remained virtually clear of acne. A second course of isotretinoin therapy was reported for 23% of the patients, and 16% had received antibiotics.¹⁹

Several adverse effects of isotretinoin have been described, including but not limited to dry skin, lips, and mucous membranes; sun sensitivity; disturbance of night vision; skeletal and muscular pain; pseudotumor cerebri; mood swings; and increased triglycerides and cholesterol. Fetal exposure to isotretinoin must be avoided, as the drug is a known teratogen and can cause serious birth defects. A mandatory closed drug

distribution program (iPledge) has been developed to reduce the risk of fetal exposure while making isotretinoin available to patients who need it for severe acne.²⁰ The iPledge program requires registration of all wholesalers, pharmacies, prescriptions, and patients who participate in the distribution of isotretinoin. In addition, documentation of negative pregnancy test results for female patients of childbearing potential is required before starting isotretinoin, at each monthly visit during treatment, and for up to 1 month after discontinuation of treatment.

Many patients are interested in the use of light therapy for acne. Several different types of light therapy have been developed, which act by different mechanisms and are sometimes combined in various treatment regimens.²¹⁻²³ A high-intensity, narrow-band blue light (405–420 nm) system reduces primarily inflammatory lesions. A broad-spectrum (430–1200 nm) light targets porphyrins that are produced within *P. acnes* bacteria. A 1450-nm carbon dioxide laser affects dermal water to induce thermal destruction of sebaceous glands. A pulsed nonablative laser (Er:YAG) can reduce the appearance of scarring by stimulating collagen formation. More recently, photodynamic therapy with 5-aminolevulinic acid is an additional emerging treatment modality. These procedures are usually performed by dermatologists who also have a strong interest in cosmesis, and are usually not covered by insurance.

USING ACNE THERAPY IN CLINICAL PRACTICE

It is important for patients to understand that the therapeutic response for all of these agents is relatively slow. Acne therapy requires consistent, long-term treatment application to control the pathologic processes that cause disease. Patients should be instructed that treatment is intended to control acne symptoms and is not a cure. In order to prevent acne recurrence, they should continue with treatment even after their acne lesions begin to improve. The process of gradual retinization with topical retinoids that was described earlier in this article must be explained to patients at the beginning of therapy to avoid poor treatment adherence and treatment failure. Patients should understand that an initial flare of acne at the beginning of treatment is possible, but should not prompt discontinuation of medication. Combination treatments should be considered when possible to

address multiple pathologic mechanisms and improve adherence. Finally, patients should be evaluated after 2 to 3 months to assess treatment response, adverse effects, and adherence to treatment.

CONCLUSIONS

Acne is a very common condition that is associated with considerable discomfort and psychological distress. Acne lesions form as a consequence of the interaction of several interrelated pathogenic processes, including both inflammatory and noninflammatory components. For mild acne, benzoyl peroxide or the combination of benzoyl peroxide and a topical antibiotic (which provides both antibacterial and comedolytic effects) are effective for both inflammatory and noninflammatory lesions. Retinoids may be combined with benzoyl peroxide or a benzoyl peroxide/antibiotic combination product if initial treatment does not produce an adequate response. The comedolytic effect of topical retinoids is often highly effective against noninflammatory lesions, and may also improve inflammatory lesions indirectly by inhibiting microcomedone formation.

Oral antibiotics are usually used for patients with moderate-to-severe acne who have not improved adequately with combination topical therapy, or for patients with widespread acne or acne affecting body surfaces where application of a topical agent would be difficult (eg, the back). Severe acne is often treatable by family physicians using a vigorous combination of the treatments mentioned in this article. Antibiotic resistance with topical antibiotics may be reduced by the use of a benzoyl peroxide combination product. Patient education is important to establish reasonable expectations and to maintain long-term treatment adherence. Referral to a dermatologist should be considered for patients who do not respond to treatment or who are considered to be at significant risk of scarring.

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