THE IMPORTANCE OF EARLY DIAGNOSIS AND TREATMENT OF ACNE*

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ABSTRACT

Several topical and systemic agents are available for acne treatment. Commonly used topical therapies include retinoids, benzoyl peroxide, antibiotics, and products that combine 2 or more active ingredients. Oral antibiotics, hormonal contraceptives, and isotretinoin are usually used for the treatment of severe acne, or for patients with mild-to-moderate acne that has not responded to other therapy. The selection of treatment for an individual patient is influenced by several factors, including acne severity, the types of lesions present, psychosocial impact, and patient preferences. Topical retinoids significantly improve inflammatory and noninflammatory acne lesions. Skin irritation may be reduced by beginning therapy on an every-other-day basis for the first few weeks to allow adaptation to the retinoid. Benzoyl peroxide rapidly reduces bacteria that cause inflammatory acne, and accelerates the rate of acne clearance when combined with a topical antibiotic. The combination of a benzoyl peroxide and a topical antibiotic also reduces the likelihood of antibiotic resistance. Oral antibiotics have long been used for acne therapy. These agents are generally well tolerated, although antibiotic resistance is a significant and growing concern with oral antibiotics. Oral isotretinoin is a very effective antiacne medication that has significantly improved the quality of life of many patients. It is associated with several important adverse effects, and the use of isotretinoin by female patients of childbearing potential is carefully regulated because of the substantial risk of birth defects. Patient education is essential to establish realistic expectations about acne treatment and to help maintain treatment adherence.

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As described in the article by Dr Mancini, the pathogenesis of acne is a complex process that includes abnormal keratinization of the follicular lumen, follicular plugging and distention, colonization of follicles by *Propionibacterium acnes*, and an inflammatory response. A large number of topical and systemic medications are available for the treatment of acne. Commonly used topical therapies include benzoyl peroxide, retinoids, and antibiotics. Other topical agents that are used less often include azelaic acid, glycolic acid, salicylic acid, sodium sulfacetamide, nicotinamide, and zinc. Commonly used oral therapies include antibiotics, isotretinoin, and oral contraceptives. The biological targets of the various acne medications are summarized in Figure 1.[1]

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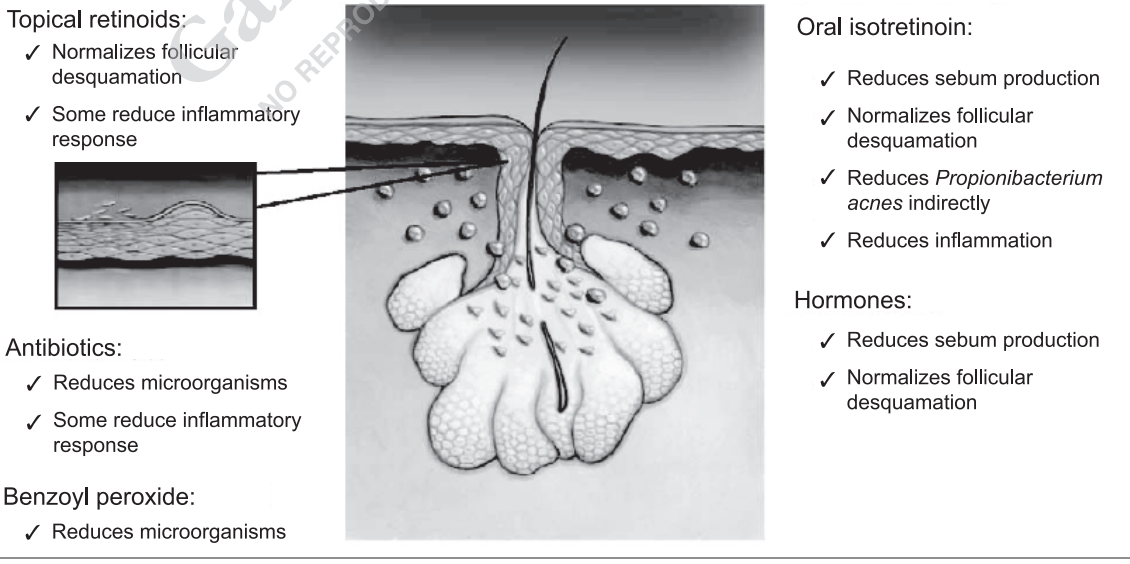
The selection of an acne treatment strategy is influenced by several factors, including the pathologic characteristics of the lesions (eg, the presence of comedones, inflammation, cysts, or nodules), lesion severity and extent, and the presence of scarring or postinflammatory pigmentation. Treatment is also influenced by the psychosocial disability experienced by the patient. The psychological impact of acne varies considerably from patient to patient, even for individuals who have similar acne severity. Some patients are very distressed by relatively mild acne, and may require more intensive therapy. Therefore, it becomes important to question patients regarding their feelings about their acne symptoms.

In general, acne may be described as mild, moderate, or severe.[2] Mild acne is defined as comedonal acne with no more than a few papules or pustules and an absence of nodules. Moderate acne is characterized by a greater number of papules and pustules, with or without a small number of nodules. Severe acne is defined as the presence of numerous or widely distributed papules and pustules and many nodules. This form of acne is frequently associated with scarring. Topical medications are generally used as first-line therapy for patients with mild-to-moderate acne, and are also used in combination with oral medications for patients with severe acne.[3] Systemic therapies are generally used for patients with severe acne, or for patients with mild-to-moderate acne who have not responded adequately to topical treatments. Combining medications that act on different mechanisms of acne pathogenesis is an important principle of acne therapy.

Topical Therapy

Topical retinoids are a mainstay of acne therapy, and are especially effective for patients with comedonal acne. These agents suppress abnormal keratinization and help to normalize the flow of sebum from the sebaceous gland to the surface of the skin. Retinoids also help to reduce inflammation of follicular epithelial cells.[1] Several topical retinoids are used for acne therapy, in a variety of concentrations and vehicles. Tretinoin has been available longer than the other retinoids, and is prescribed in cream, gel, liquid, microsphere gel, and polymerized cream or gel formulations, in concentrations from 0.01% to 0.1%. Adapalene is available in cream and gel formulations, in concentrations from 0.1% to 0.3%. Tazarotene is available in cream and gel formulations at concentrations of 0.05% to 0.1%. Several studies have documented that topical retinoids significantly improve both inflammatory and nonin-

Figure 1. Mechanisms of Action for Common Acne Therapies



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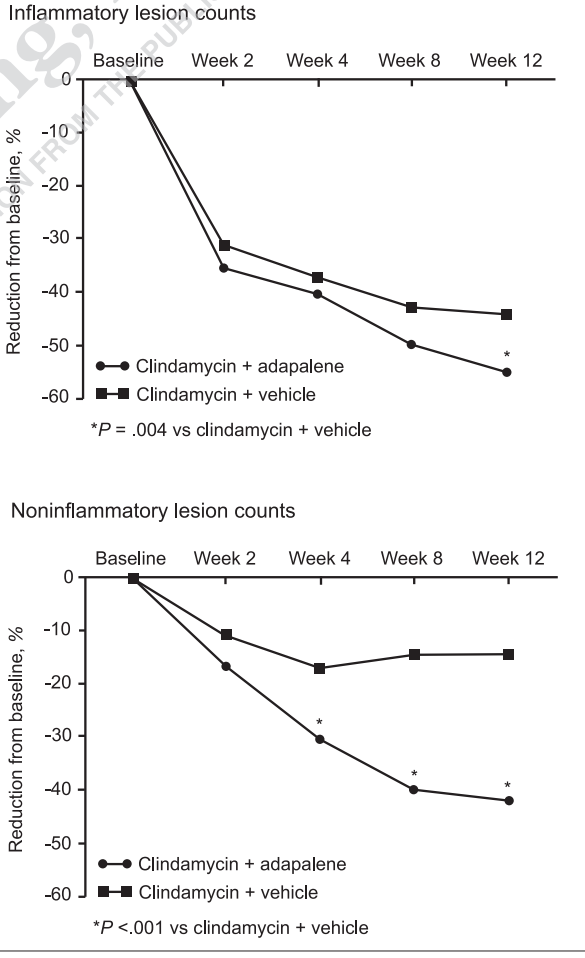
flammatory acne lesions.[4,5] Placebo-controlled clinical trials of these agents have reported reductions of approximately 40% to 50% in the number of acne lesions after 12 weeks of treatment.[1]

Topical retinoid therapy often produces significant skin irritation, especially during the first 2 weeks of treatment. Irritation may be reduced by a process of gradual retinization, in which the frequency of administration is reduced during the first 2 weeks of therapy (eg, to every other day). Patients should be reassured that the skin reaction to retinoid therapy is experienced by nearly all patients, and encouraged to remain on therapy until improvement occurs. Another option for patients with an intolerable response to a topical retinoid is to apply the medication for a limited number of hours per day. For example, the medication may be applied when the patient returns home from school in the afternoon, and then washed off before bedtime. All of the topical retinoids can cause significant photosensitivity, and are therefore often applied at night. Early formulations of tretinoin were somewhat unstable and could be inactivated if applied concurrently with other topical medications. Newer formulations of the topical retinoids, in which the active ingredient is incorporated into a microsphere or slow-release polymer vehicle, possess better stability and are also less likely to cause photosensitivity or irritation.[3]

Formulations containing benzoyl peroxide are very effective for inflammatory acne, and are widely used for the treatment of papules and pustules. Benzoyl peroxide is an antibacterial agent that rapidly reduces *P acnes* on the skin surface by approximately 90%, resulting in rapid improvement in inflammatory acne lesions without causing bacterial resistance.[1] Several over-the-counter topical benzoyl peroxide formulations are widely available, and many are popular with patients who have acne. However, it should be noted that these nonprescription products contain a maximum of only 2.5% benzoyl peroxide, which is substantially lower than concentrations that are available with prescription formulations. In addition, nonprescription products penetrate follicles relatively poorly, and thus suppress *P acnes* formation primarily at the skin surface. In contrast, the vehicles that are used in the formulation of prescription benzoyl peroxide permit greater penetration of the product into follicles, and are thus more effective for the suppression of *P acnes*.[6]

Combination topical therapy provides the opportunity to treat different pathophysiological processes simultaneously, increasing the potential for greater efficacy than monotherapy. For example, the combination of a topical retinoid and a topical antibiotic has been shown to produce greater reduction in acne severity than a topical antibiotic alone (Figure 2).[7] Adherence is also improved when patients apply only a single treatment, and patient copays may be lower. Products that combine benzoyl peroxide with a topical antibiotic (usually erythromycin or clindamycin) are mainstays of acne therapy, and are indispensable for the management of many patients.

Figure 2. Treatment with the Combination of a Topical Retinoid and Topical Antibiotic



Treatment with the combination of a topical retinoid and a topical antibiotic resulted in significantly greater reduction in inflammatory and noninflammatory lesions over 12 weeks in patients with acne.
Reprinted with permission from Wolf et al. *J Am Acad Dermatol.* 2003;49(3 suppl):S211-S217.[7]

The addition of benzoyl peroxide to a topical antibiotic product has been shown to reduce *P acnes* proliferation more rapidly and more completely than a topical antibiotic,[8] and to provide greater improvement in acne symptoms than either topical benzoyl peroxide or topical antibiotic alone.[9] For example, Lookingbill et al reported the combined results of 2 double-blind clinical trials that examined the efficacy and tolerability of combination therapy with benzoyl peroxide and topical clindamycin in patients with mild-to-moderate acne.[9] A total of 334 patients were randomized to treatment with 1 of 4 topical agents—clindamycin 1% gel, benzoyl peroxide 5% gel, a combination gel containing clindamycin 1% and benzoyl peroxide 5%, or placebo gel. The combination gel was superior to placebo for all outcome measures, and was superior to either monotherapy option for nearly all outcome measures studied (including clinician rating of good or excellent response, reduction in inflammatory lesions, and mean global improvement scores; Figure 3). Products that contain benzoyl peroxide and a topical retinoid are also effective for acne therapy.[10]

Combination products may also help to reduce the problem of antibiotic resistance. Recent guidelines for acne management that were developed by the American Academy of Dermatology noted that although topical antibiotics are effective acne therapies, antibiotic resistance is common when these agents are used as acne monotherapy.[11] The use of a combination product that contains a topical antibiotic and benzoyl peroxide has been shown to significantly reduce antibiotic-resistant bacteria compared to a topical antibiotic alone.[12,13] A randomized, double-blind clinical trial that compared several different oral and topical acne treatment regimens in patients with mild-to-moderate acne found that combinations of benzoyl peroxide and topical antibiotics produced improvements that were similar in magnitude to oral tetracyclines, but were less likely to cause the proliferation of antibiotic-resistant *P acnes* bacteria.[14]

Oral Acne Therapy

Oral antibiotics are recommended for the treatment of moderate-to-severe acne, and for treatment-resistant inflammatory acne.[11] Antibiotics that are most often used in acne therapy include tetracycline (250–500 mg twice daily), doxycycline (50–100 mg once or twice daily), and minocycline (50–100 mg once or twice daily). These antibiotics should always

Evidence-Based Practice Recommendation

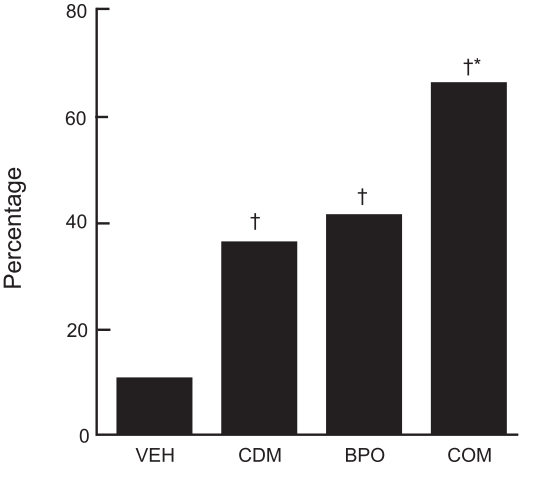
I. Practice Recommendation: Systemic antibiotics are appropriate for the treatment of moderate-to-severe acne or for patients with treatment-resistant forms of inflammatory acne.

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: The American Academy of Dermatology expert consensus panel concluded that systemic treatment with antibiotics is part of the standard of care for patients with moderate-to-severe acne or treatment-resistant acne. The panel identified several clinical trials that have demonstrated significant improvements in acne with tetracyclines and macrolides. The opinion of the expert consensus panel was that doxycycline and minocycline may be more effective than tetracycline.

Figure 3. Percentage of Patients with Good or Excellent Global Response After 11 Weeks of Therapy with VEH, CDM, BPO, or COM



*Difference compared to CDM or BPO is statistically significant.
†Difference compared to VEH is statistically significant.
BPO = topical benzoyl peroxide; CDM = topical clindamycin; COM = combination; VEH = vehicle cream.
Reprinted with permission from Lookingbill et al. *J Am Acad Dermatol.* 1997;37:590-595.[9]

be taken with a full glass of water in order to decrease gastritis. Erythromycin (250–500 mg twice daily) is also used in some cases, although the effectiveness of erythromycin has decreased over the past several decades as antibiotic resistance has become more common.[11] Erythromycin is generally recommended for patients who cannot use tetracyclines (eg, pregnant women and young children who would be at risk of damage to the skeleton or the teeth).[11] Antibiotic resistance is a significant concern with all of the oral antibiotics. Adverse events associated with oral antibiotics include photosensitivity, headache, dizziness, and tooth staining. Pseudotumor cerebri is a rare complication of all of the cycline-based antibiotics.[15] This condition is characterized by increased intracranial pressure, resulting in neurologic symptoms that include severe headache, nausea, and visual disturbance.[15] Pseudotumor cerebri may cause severe permanent visual loss if not recognized early.[16]

Patients with severe acne often require intensive treatment to improve lesions and reduce the risk of scarring. Treatment usually consists of a combination of benzoyl peroxide, topical antibiotics or retinoids, and oral antibiotics. Oral contraceptives or oral isotretinoin should be considered for patients who have nodular or cystic acne that has failed to respond to oral antibiotics. Clinical trials have demonstrated that estrogen-containing oral contraceptives reduce acne severity in female patients.[1] Some oral contraceptives are approved by the US Food and Drug Administration (FDA) for acne therapy (eg, norgestimate and ethinyl estradiol, norethindrone acetate and ethinyl estradiol, and drospirenone and ethinyl estradiol), and others may also be effective for this purpose.[11]

Although there are several challenges associated with isotretinoin use, it is also a very powerful treatment option for patients with severe acne, and it has the potential to substantially improve quality of life for appropriate patients. Oral isotretinoin is approved for the treatment of severe, treatment-resistant nodular acne. Expert consensus guidelines also recommend oral isotretinoin for acne that is less severe but resistant to other treatments for patients at high risk of scarring, or for patients with marked psychological distress about their acne.[11] Isotretinoin produces a number of therapeutic effects in acne care, including reversal of hyperkeratosis, reduction of sebum levels, suppression of *P acnes* proliferation, and improvement of inflammation.[17] Most importantly, isotretinoin is unique among acne therapies due to its ability to alter the progression of acne by inducing long-lasting suppression of the sebaceous glands.[18]

Isotretinoin is a teratogen that must not be administered to female patients of childbearing potential unless they are enrolled in the iPLEDGE isotretinoin distribution program. iPLEDGE is a rigorous risk-management program that requires documentation of 2 negative pregnancy tests and 2 forms of contraception for all female patients of childbearing potential before dispensing of the medication by a pharmacist, and is closely monitored by the US FDA.[19] Participation is required not only by physicians, but also by pharmacists, drug wholesalers, and everyone who is involved in the distribution of isotretinoin. Pregnancies in the iPLEDGE program have occurred almost entirely among college-educated female patients who failed to take their oral contraceptives every day, rather than among adolescent females. Isotretinoin is also associated with several significant adverse events, including headache, cheilitis, dry skin, hyperlipidemia, an initial flare of acne, alopecia, myalgia, fatigue, pseudotumor cerebri, visual disturbances or eye irritation, and depression.[20,21] Although relatively costly, isotretinoin may result in lower overall treatment cost by reducing the number of physician visits and the use of other prescription medications.

The Importance of Patient Education in Acne Therapy

Acne is rarely cured, and continued treatment for 6 to 8 weeks is usually required to sustain improvements in acne lesions. In treating papular acne, it is important to try to minimize the risk of inflammatory skin changes. One particular concern is the risk of postinflammatory hyperpigmentation or hypopigmentation in patients of color. These temporary discolorations of the skin surface are often perceived by patients as scarring. Educating patients that these changes reflect only transient discoloration of the skin surface, and not damage to the skin itself, is an important part of acne therapy. In addition, patients with acne of the back or the chest should understand that treatment of these areas is more difficult than treatment of the face, and that additional time and effort will probably be required to attain clearing of acne that affects these surfaces. In many cases, patients are visiting the office for another condition, but not for treatment of acne.

Offering treatment for the acne may be very beneficial, especially if the patient is at significant risk of scarring. It is also important to tailor the therapy to the patient's preferences, as some patients may be unwilling to use certain therapies. Patients often have unrealistic expectations about acne therapy, and especially about the time required to produce improvement. Many patients expect to see improvement in acne symptoms within a few days. Setting realistic expectations is especially important with teenage patients, who may decide to discontinue treatment if acne has not improved within a few days of beginning treatment.

Conclusions

Several topical and systemic agents are available for acne therapy. An approach to acne therapy, as described in recent consensus guidelines developed by an international consensus committee of experts in the diagnosis and management of acne, is summarized in the Table.[3] Combining acne medications with different mechanisms of action may help to improve efficacy, prevent adverse effects, reduce antibacterial resistance, and enhance patient satisfaction. Patient education is important to establish realistic expectations about treatment outcomes, and to help patients remain adherent to acne therapy.

Evidence-Based Practice Recommendation

II. Practice Recommendation: Oral isotretinoin is a potent teratogen that should be administered only by physicians who are knowledgeable about its appropriate use and monitoring.

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 consensus guideline development panel convened by the American Academy of Dermatology reviewed the appropriate use of several acne therapies, including the use of oral isotretinoin. The panel noted that oral isotretinoin is an effective option for patients with severe acne or for selected patients with less severe disease who are at risk of scarring. Due to the risk of birth defects, female patients of childbearing potential must only receive oral isotretinoin if they are participating in the iPLEDGE pregnancy prevention program.

Table. Acne Treatment Algorithm

	Mild		Moderate		Severe, Nodular
	Co medonal	Papular/Pustular	Papular/Pustular	Nodular	
First-line therapy	Topical retinoid	Topical retinoid + BPO or BPO/AB	Topical retinoid + oral antibiotic + BPO or BPO/AB	Topical retinoid + oral antibiotic ± BPO or BPO/AB	Oral isotretinoin
Alternatives	Salicylic acid			Oral isotretinoin	Oral antibiotic + topical retinoid + BPO or BPO/AB
Alternatives for female patients			Hormonal therapy + topical retinoid ± BPO or BPO/AB	Hormonal therapy + topical retinoid ± BPO or BPO/AB	Hormonal therapy + oral antibiotic + topical retinoid ± BPO or BPO/AB
Maintenance therapy	Topical retinoid ± BPO or BPO/AB		Topical retinoid ± BPO or BPO/AB		Topical retinoid ± BPO or BPO/AB

AB = topical antibiotic; BPO = topical benzoyl peroxide.
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