ABSTRACT

Acne lesions develop as the result of an inflammatory response to bacterial colonization of skin follicles that have become obstructed and swollen with sebum. *Propionibacterium acnes* bacteria digest triglycerides that are a principal component of sebum and release fatty acids, chemotactic factors, and other molecules that stimulate skin inflammation and the formation of pustules. Acne management is a long-term process that requires considerable patient education regarding the nature of the disorder and the likely effectiveness of acne treatments. Patients often have misconceptions about the importance of diet, cleanliness, or other disease factors, and they may have unrealistic expectations about the effectiveness of therapy. Several topical and systemic acne therapies are available. Topical antibiotic products have lost some of their effectiveness in recent years as a result of antibiotic resistance. Combination products that include benzoyl peroxide and a topical antibiotic (eg, benzoyl peroxide and clindamycin or erythromycin) reduce acne-causing bacteria and the development of antibiotic-resistant strains. Topical retinoids are a mainstay of acne treatment and can be used to reduce the need for antibiotics during long-term maintenance therapy. Systemic treatments include antibiotics of the tetracycline family (especially minocycline and doxycycline), oral isotretinoin, and hormonal therapy with spironolactone and oral contraceptives. Tetracycline antibiotics usually are effective for treating severe acne and are generally well tolerated. Common side effects include phototoxicity and gastrointestinal upset; other side effects, such as skin pigmentation or lupus-like symptoms, are rare. Oral isotretinoin is effective for many patients who do not respond to other therapies. It is a potent teratogen, and adequate contraception and patient education are essential. Isotretinoin-induced flares of severe acne can be avoided by starting treatment at a low dose and adding prednisone for the first month. The relationships between isotretinoin use and bowel disease, bone turnover, and depression are controversial. The appropriate selection of oral and systemic therapies based on the type and severity of acne lesions can safely and effectively improve symptoms, even for many patients with severe acne. *(Adv Stud Nurs. 2005;3(7):228-233)*

Acne lesions develop in a 2-stage process. The first stage is the formation of a comedo (a blackhead or a whitehead) as a result of obstruction of a follicle. Under normal circumstances, the follicle provides a channel for sebum, which is produced by the sebaceous gland at the follicle base, to be released at the skin surface. In acne, abnormal keratinization occurs within the follicle, and the cells that line the inner surface of the follicle begin to separate from the follicular canal in large sheets. The combination of these keratinized cells and accumulating sebum obstruct the follicle and prevent the release of sebum to the skin surface, causing the follicle to inflate and pro-
The microcomedo continues to grow until it has become a visible comedo (Figure). A blackhead is a comedo with an opening to the skin surface, whereas a whitehead has no opening to the skin. By the time a fully developed comedo has formed, the sebaceous gland has stopped secreting sebum.

The second stage of acne formation reflects an inflammatory process in which an immune response develops to the colonization of the microcomedo by bacteria. It should be noted that the microcomedo, and not the fully developed comedo, is the precursor to an acne lesion. This was demonstrated by Kligman more than 30 years ago in studies in which serial skin photographs were taken of acne lesions. These photographs showed that the large, easily visible blackheads and whiteheads did not develop into acne lesions. Rather, the lesions developed in skin regions that were free of visible comedones. It was subsequently shown that acne lesions develop as a result of inflammation in response to the growth of the bacterium *Propionibacterium acnes* within microcomedones. *P. acnes* is a member of the normal flora that lives on the skin wherever sebaceous glands are numerous, which is primarily the head and upper trunk.

*P. acnes* bacteria release a lipase that degrades the triglycerides in sebum to free fatty acids. These bacteria also release chemotactic factors and other inflammatory molecules that stimulate inflammation and the infiltration of neutrophils, resulting in pustule formation. Sebum secretion is controlled by androgens, which is why acne often begins at adrenarche or, more typically, at puberty.

Several types of acne lesions have been described. Comedonal lesions are plugs with little inflammation. Pustular lesions are superficial papules with minimal scarring. Papular lesions are deeper inflammatory lesions that may scar. Nodular lesions are characterized by very deep inflammation and scarring. Conglobate lesions occur when nodules merge beneath the skin surface and become connected by a sinus tract. These tracts often become epithelialized. They are very resistant to typical acne therapy and often require excision.

**Principles of Acne Therapy**

Acne is a chronic disease, and the management of acne is a long-term process. It is essential that the patient understands that treatment will take time and immediate improvement in acne severity is unlikely. The consequences of acne are not limited to the skin. Acne typically occurs at an age when adolescents are very sensitive about their identities and concerned about their physical appearance. The psychosocial consequences of acne extend even into adulthood. For example, it has been shown that individuals with a history of severe acne are more likely to have employment problems as adults. Cleanliness is not a significant factor in the development of acne. Scrubbing the skin is unlikely to make acne better and may actually make it worse by traumatizing the skin. Diet has little or no effect on acne, and no studies have ever clearly shown that chocolate, fat, or other dietary factors significantly affect acne severity.

Patient adherence to therapy is a significant problem. Long-term treatment is required to produce the greatest improvement in acne lesions, but the available treatment options often are not completely effective, and they require a considerable period of time to work. Therefore, patients with acne require a good deal of education to understand the nature of the disorder, how the treatments work, what side effects to expect, and how long it will take for symptoms to improve. Patient education materials are available online at the American Academy of Dermatology Web site. Adherence also is complicated by the fact that patients...
often require several different medications because most of the agents do not work well as monotherapy. With teenaged patients, parents often worsen the situation by frequently reminding the patient to use the medication. This may create a situation in which the medication becomes the focus of rebellion, leading to treatment discontinuation and poor outcomes.

**Treatment Options**

Several topical and oral medications are available for the management of acne (Table 1). The topical antibiotics erythromycin and clindamycin were effective in the late 1970s, but efficacy has decreased in recent years with the emergence of antibiotic-resistant bacterial strains. Benzoyl peroxide is effective, but it can stain or bleach clothing. Combination products that use benzoyl peroxide, such as benzoyl peroxide and clindamycin or erythromycin, are also effective for inflammatory acne. The combination of benzoyl peroxide and clindamycin produces approximately a 90% reduction in acne-causing bacteria after 1 day and reduces the development of antibiotic-resistant bacteria.

The use of a topical retinoid for long-term maintenance therapy is one of the most important components of treatment for patients with moderate to severe acne. Topical retinoids, which are vitamin A derivatives, include medications such as adapalene and tazarotene. These agents suppress inflammation and the development of new microcomedones, which allows acne maintenance with little need for additional antibiotics. However, these agents are not very effective as monotherapy for the initial treatment of acne lesions because they require several weeks to work. They are most effective when used with antibiotics early in the course of treatment. Topical retinoids work well for most patients, but they may not be well suited for the small number of patients with very irritable skin (eg, eczema or seborrheic dermatitis) or those with a great deal of sun exposure. The benefits of long-term maintenance therapy with topical retinoids were demonstrated in a study of tazarotene and minocycline, although similar results would be observed with any mixture of retinoid and oral antibiotic. Patients were treated with antibiotic and retinoid topically for 12 weeks and then randomized to tazarotene, minocycline, or both for an additional 12 weeks of maintenance therapy. The severity of acne remained similar for all 3 maintenance treatments (Webster et al, manuscript in preparation). The use of topical retinoids also discourages postinflammatory hyperpigmentation in individuals with pigmented skin.

Systemic therapy may be required for patients with deep scarring acne lesions, acne that covers a large body area, or acne that has been resistant to previous therapy. Patient preference is also an important consideration when selecting topical or systemic treatment: some patients will prefer topical agents and others will prefer oral medications. Young men, in particular, may prefer not to use topical creams. Antibiotics of the tetracycline family, of which minocycline and doxycycline are the most potent, are often used for oral acne treatment. Oral isotretinoin is very effective for severe acne and is discussed in more detail later in this article. Other possible systemic treatments include hormonal therapy with oral contraceptives and spironolactone, which is an androgen blocker in addition to its diuretic effects. Acne is significantly affected by androgen production; therefore, hormonal therapy is appealing as a potential treatment strategy. However, none of the available treatments are very effective at blocking the effects of androgens. Hormonal therapy (eg, spironolactone at a dosage of 75–100 mg/day plus an oral contraceptive) should be considered for women who are clearly virilized. A pelvic examination is unnecessary when contraceptives are used for acne treatment. Any sexually active woman should have regular pelvic examinations.

**Issues with Antibiotics**

The inappropriate use of antibiotics is a potential
cause for concern and has been discussed in the popular press and professional publications. Although it is reasonable to be concerned about antibiotic overuse, these agents are a mainstay of acne treatment, and they help to relieve the symptoms and considerable psychosocial impact of acne for many patients. Tetracycline antibiotics improve the symptoms of acne by several different mechanisms. They reduce the proliferation of *P. acnes* bacteria and inhibit its inflammatory effects, including the release of chemotactic factors that promote the infiltration of neutrophils.1,11 Tetracyclines also inhibit the function of the lipase enzyme that *P. acnes* bacteria require to digest sebum12 and produce direct anti-inflammatory effects by reducing the production of inflammatory mediators, such as nitric oxide.13 For these reasons, tetracyclines are more effective than erythromycin for the treatment of acne. Although oral antibiotics are commonly used to treat acne, it is difficult to find high-quality, well-controlled clinical trials that have demonstrated the effectiveness of these and other acne medications. One reason for this is that all of the acne drugs (and especially the retinoids) often induce an irritant response that makes it impossible to perform a clinical trial that is completely blinded because patients who receive active medication often develop dry skin and chapped lips that unblind the study. Health maintenance organizations may try to avoid paying for these therapies because of the “limited data” supporting their effectiveness.

Minocycline is considered the most potent of the tetracycline family of antibiotics; doxycycline is nearly as potent, and tetracycline is the least potent.1 Most clinicians who prescribe these medications think that minocycline is more effective than other tetracycline antibiotics for treatment of more severe acne, even though clinical trials comparing minocycline and doxycycline have generally found that they produce similar effectiveness. The reason for this discrepancy is probably related to the characteristics of the patients who are enrolled in randomized clinical trials of acne treatments. Patients who volunteer for random assignment to treatment with the possibility of receiving placebo are typically not the patients with the most severe, poorly controlled acne. These patients may respond equally well to doxycycline or minocycline, whereas minocycline may be more effective in patients with more severe acne who are less likely to enroll in randomized studies. Oral macrolides are no longer very useful for acne treatment, although topical macrolides are somewhat effective.

The use of antibiotics in acne therapy is generally safe, although adverse effects are possible. Dose-dependent phototoxicity occurs in some patients, but this is rare and can usually be avoided by encouraging patients to use sunscreen. Gastrointestinal upset and dizziness are unpredictable side effects that can sometimes be improved by taking the medication with food, but may require discontinuation. A less common but potentially serious complication is pigmentation of the skin by minocycline, especially in areas of inflammation. Pigmentation of the ears, teeth, and cartilage also are possible and can be very difficult to reverse. Minocycline can also produce a rare lupus-like hypersensitivity reaction.14 Pseudotumor cerebri (medication-induced intracranial hypertension) is very rare and thought to be most common with minocycline and doxycycline.15 Rapid evaluation is necessary for a patient taking any tetracycline antibiotic who develops a severe headache or visual disturbances while using minocycline.

Antibiotic-resistant bacteria are becoming more common in the environment and are increasingly the cause of acne, which has made it more difficult to treat acne using some antibiotics. Although rarely done in clinical practice, performing a culture in a patient with acne that does not respond to treatment often reveals the presence of a resistant strain, and switching to an antibiotic to which the organism lacks resistance can improve the treatment outcome. However, *P. acnes* is not routinely cultured because it is difficult to grow in the laboratory. Modifications to the treatment regimen for poor response are usually done empirically. Switching to a different class of antibiotic or to isotretinoin, or adding benzoyl peroxide or a benzoyl peroxide/clindamycin combination formulation, are all reasonable approaches to the problem of resistance. The use of antibiotics for acne therapy also can alter the resistance patterns of other organisms. For example, the prevalence and antibiotic resistance patterns of *Streptococcus pyogenes* and *Staphylococcus aureus* were examined in patients with acne who were using or not using antibiotic therapy.16 *S. pyogenes* colonization increased from 10% in patients not using antibiotics to 33% of patients using tetracycline antibiotics. Antibiotic-resistant bacterial strains were identified in 20% of untreated patients and 85% of patients using antibiotics. These findings underscore the importance of topical retinoids as a means to move patients from long-term antibiotic therapy. Antibiotic resistance also can be reduced by using full-dose antibiotic therapy rather than reduced doses and by limiting the duration of therapy (usually to 3–6 months).
ISOTRETINOIN

Isotretinoin is effective for patients who do not respond to other treatments, such as patients with severe nodular acne or extensive acne on the back or chest. The principal mechanism by which isotretinoin improves acne is the suppression of sebum. Sebum production is reduced to perhaps 10% of normal levels within 1 to 2 months and remains suppressed long after treatment is discontinued.\(^\text{17}\) Isotretinoin also suppresses \textit{P. acnes} proliferation, chronic inflammation, and the follicular keratinization that contribute to comedo formation.\(^\text{18}\) For patients taking isotretinoin at an adequate dosage (eg, 1 mg/kg per day for 4–6 months), approximately 80% remain acne-free for several years after cessation of treatment.\(^\text{19}\) At lower dosages, the recurrence rate is higher.

There are several adverse effects associated with isotretinoin.\(^\text{20}\) Sometimes these adverse effects can be reduced by lowering the dose, although it then may be necessary to increase treatment duration. Lips and skin can become very dry, especially during the winter. Triglycerides increase in approximately 25% of patients, as isotretinoin may uncover a type IV hyperlipidemia. Acne flares also are possible during the first and second weeks of treatment. Less commonly, isotretinoin may produce elevated creatine kinase release from muscle. Elevated transaminases may mistakenly be attributed to liver damage; however, specific measures of liver function (eg, liver-specific enzyme gamma-glutamyl transferase) are typically normal. Dry eyes and impaired night vision may occur, although patients rarely perceive these as serious problems if they are warned to anticipate them at the beginning of treatment.

Acne fulminans was once a relatively rare disorder, but it has become more common as a result of inappropriate isotretinoin use. Isotretinoin can cause acne flares that are characterized by severe ulcerative, pustulating lesions. Many clinicians who are not familiar with isotretinoin make the problem worse by increasing the isotretinoin dose at the first sign of acne flare. This higher dose only makes the problem worse by increasing the isotretinoin dose at the beginning of treatment.

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Acne is an inflammatory skin disease that is caused by an immune response to the colonization of microcomedones by the skin bacteria \textit{P. acnes}. Topical and...
Table 2. Topical Treatment Regimens for Acne

<table>
<thead>
<tr>
<th>Acne Type</th>
<th>Treatments</th>
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<tbody>
<tr>
<td>Comedonal Acne</td>
<td>Topical tretinoin, adapalene, or tazarotene applied daily, salicylic acid, azelaic acid</td>
</tr>
<tr>
<td>Mild Papulopustular Acne</td>
<td>Benzoyl peroxide, topical gel preparations of benzoyl peroxide with clindamycin or erythromycin, oral doxycycline</td>
</tr>
<tr>
<td>Severe Papulopustular or Nodular Acne</td>
<td>Oral doxycycline or minocycline plus topical retinoid (isotretinoin, 1 mg/kg per day)</td>
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systemic antibiotics, topical retinoids, and benzoyl peroxide preparations, including clindamycin or erythromycin combinations, are effective and generally safe and well tolerated. Isotretinoin is effective for more severe acne, but it is associated with more safety concerns. A typical approach to treatment, based on acne severity, is summarized in Table 2.31

REFERENCES