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Expert Committee Recommendations for Acne Management

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SPECIAL ARTICLE

Expert Committee Recommendations for Acne Management

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ABSTRACT

In 2003, an international committee of physicians and researchers in the field of acne, working together as the Global Alliance to Improve Outcomes in Acne, developed consensus guidelines for the treatment of acne. These guidelines were evidence based when possible but also included the extensive clinical experience of this group of international dermatologists. As a result of the evaluation of available data and the experience, significant changes occurred in the management routines for acne. The greatest change arose on the basis of improved understanding of acne pathophysiology. The recommendation now is that acne treatments should be combined to target as many pathogenic factors as possible.

- A topical retinoid should be the foundation of treatment for most patients with acne, because retinoids target the microcomedo, the precursor to all acne lesions. Retinoids also are comedolytic and have intrinsic antiinflammatory effects, thus targeting 2 pathogenic factors in acne.
- Combining a topical retinoid with an antimicrobial agent targets 3 pathogenic factors, and clinical trials have shown that comination therapy results in significantly faster and greater clearing as opposed to antimicrobial therapy alone.
- Oral antibiotics should be used only in moderate-to-severe acne, should not be used as monotherapy, and should be discontinued as soon as possible (usually within 8–12 weeks).
- Because of their effect on the microcomedo, topical retinoids also are recommended as an important facet of maintenance therapy.

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Key Words
acne vulgaris, pathophysiology, retinoids, antimicrobials, combination therapy, maintenance therapy

Abbreviation
BPO— benzoyl peroxide

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THE INCIDENCE OF acne vulgaris in adolescents and young adults is exceedingly high, with ~80% of persons aged 11 to 30 years affected.[1,2] The onset of acne is typically in early adolescence; therefore, pediatricians are often the first health care providers for patients with acne and should be familiar with current recommendations about acne management. The multifactorial etiology of acne and growing public health concerns about bacterial resistance have led acne experts to reexamine the role of oral antibiotics and topical retinoids in the treatment of mild-to-moderate acne, as will be discussed herein.

PATHOGENESIS OF ACNE

The first step in developing effective therapeutic regimens for patients with acne is to understand the pathogenesis of this disorder. Acne lesions occur in the pilosebaceous unit, which consists of the hair follicle, the hair shaft, and the sebaceous gland. The initial step in all acne lesions (inflammatory and noninflammatory) is the development of the microcomedo. Four primary factors contribute to the development of acne lesions: abnormal desquamation of keratinocytes within the pilosebaceous unit, increased sebum production, proliferation of *Propionibacterium acnes*, and inflammation (Fig 1).[3]

Starting at ~7 to 8 years of age, the onset of adrenarche is heralded by an overall increase in sebum production.[4,5] Over the following years and throughout puberty, circulating androgens act locally on the sebaceous glands and are metabolized there, resulting in an increase in both the number of sebaceous lobules and the overall follicular size.[6–11] When androgens are taken up into the cell and bind to the androgen receptors, differentiation of the sebocyte begins. Gene transcription is initiated, and the sebocyte subsequently matures.[4,7,12] As the sebocyte differentiates, it ruptures and releases lipids into the sebaceous duct and follicle.[1] With the resultant seborrhea and the potential for an androgenic effect on the follicular keratinocytes, the follicle is primed for microcomedo formation.[6]

Simultaneously, the rate of desquamation of the keratinocytes at the follicular fundibulum is altered. Normally, single keratinocytes are shed into the follicular lumen for excretion.[3,6] In acne, this process is disrupted and keratinocytes accumulate, becoming interwoven with monofilaments and lipid droplets.[3,6,13–15] This accumulation of cells and sebum results in the formation of a microcomedo, the microscopic precursor to all acne lesions.[3,16]

In patients prone to acne, the pilosebaceous follicle fills with a mixture of bacteria, sebum, and keratin, and a clinically apparent lesion develops (Figs 2–5). The relative contribution of these factors determines if the lesion is noninflammatory (open comedo [blackhead] or closed comedo [whitehead]) or inflammatory (papule or pustule).[1] Inflammatory lesions are characterized by proliferation of *P acnes*, a Gram-positive anaerobe that resides in the pilosebaceous unit. The role of *P acnes* in

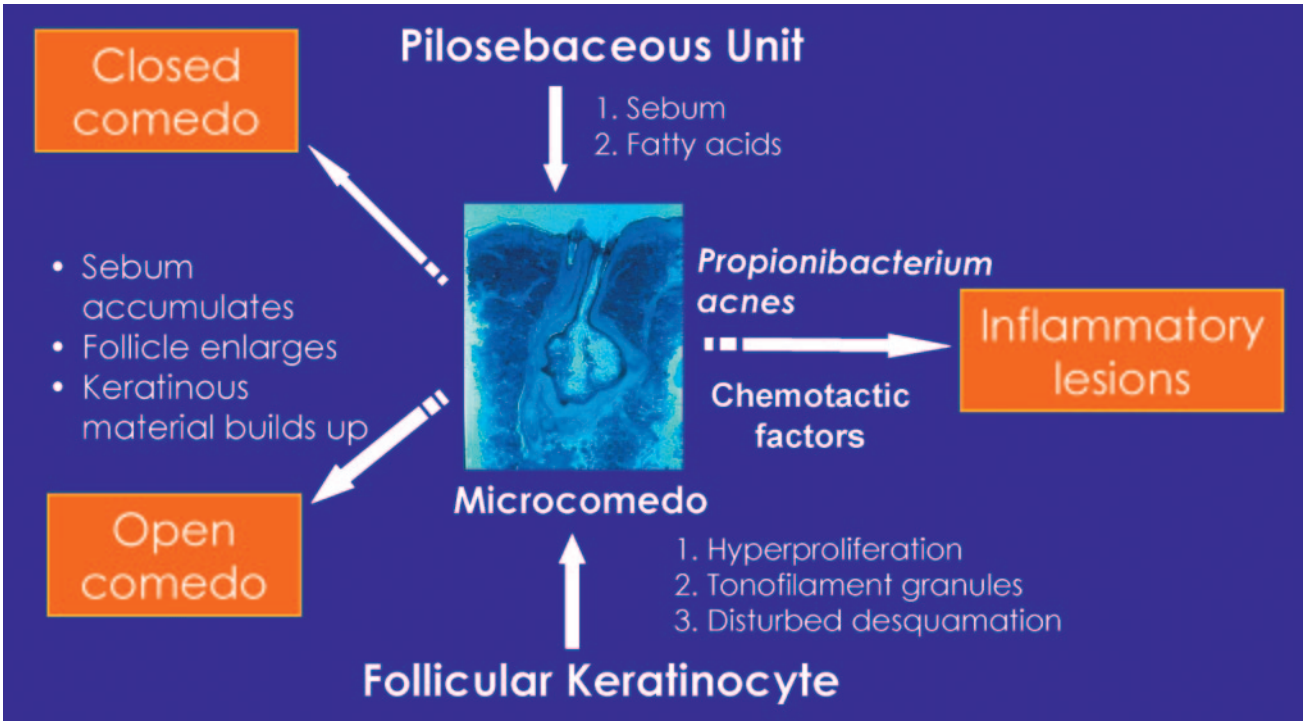

FIGURE 1
Pathogenesis of acne. (Adapted from Gollnick H, Cunliffe W, Berson D, et al. *J Am Acad Dermatol*. 2003;49[1 suppl]:S1–S37.)

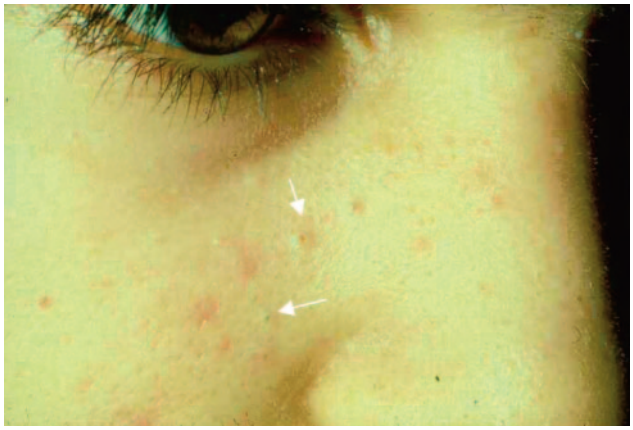

FIGURE 2
Patient presenting with open comedones (blackheads) and closed comedones (whiteheads).

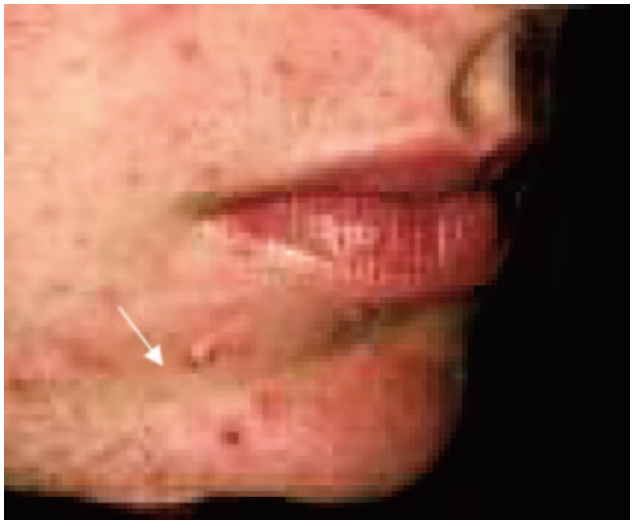

FIGURE 3
Patient presenting with acne pustules.

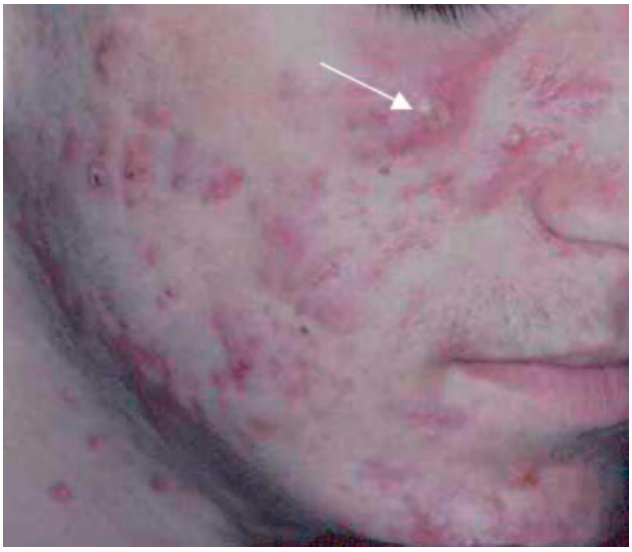

FIGURE 4
Patient presenting with acne cysts and nodules.

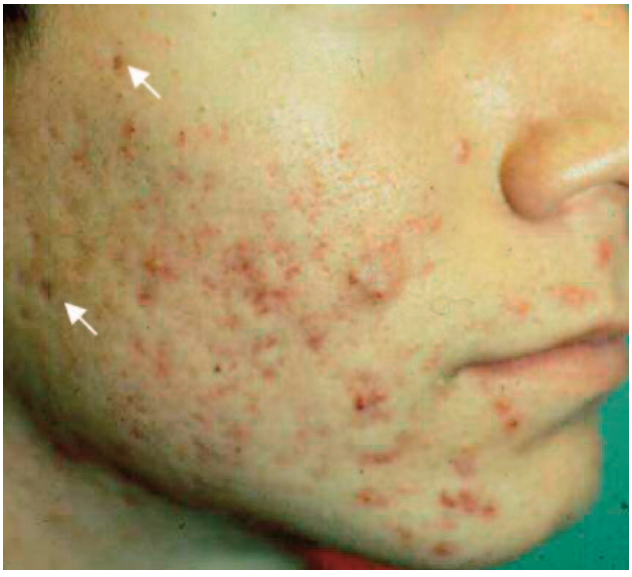

FIGURE 5
Patient with acne scars.

acne is now thought to be inflammatory rather than infectious.[3,17] Severity of acne is related to interactions between the bacterium and antibody, complement, and cell-mediated immune responses,[15,18,19] not to bacterial count on the skin surface.[17] Cellular products from *P acnes* stimulate the recruitment of CD4 lymphocytes and, subsequently, neutrophils. These inflammatory cells penetrate the follicular wall, causing disruption of the follicular barrier.[6,18,20] With the barrier compromised, lipids, shed keratinocytes, and *P acnes* organisms are released into the surrounding dermis, inciting further recruitment of inflammatory cytokines and neuropeptides, including substance P.[19,21] Reduction in *P acnes* is associated with a reduction in inflammatory mediators and clinical improvement of acne.[3,22]

ACNE TREATMENT OPTIONS

The advances in understanding of the pathophysiology of acne have led to changes in therapeutic dogma. The Global Alliance to Improve Outcomes in Acne, an international group of acne experts, recently developed evidence-based guidelines for the management of acne.[3] A treatment algorithm based on these consensus guidelines[3] is presented in Table 1.

The most noticeable change from previous algorithms is that topical retinoids now play a central role in therapy for the majority of patients with acne. Depending on the degree of inflammation, topical retinoids should be used either alone (when comedones predominate) or in combination with an antimicrobial agent. Female patients also may benefit from hormonal therapy with oral contraceptives. For severe acne, treatment with oral isotreti-

TABLE 1 **Acne Treatment Algorithm**

	Mild		Moderate		Severe, Nodular
	Comedonal	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 indicates topical antibiotic.
Adapted from Gollnick H, Cunliffe W, Berson D, et al. *J Am Acad Dermatol*. 2003;49(1 suppl):S1–S37.

noin is recommended. Isotretinoin therapy also should be considered for cases of acne that are refractory to conventional therapy with a topical retinoid, benzoyl peroxide (BPO), and oral antibiotic therapy.[3]

Topical Retinoids: The Foundation of Therapy

Topical retinoids, which in the past were reserved for patients with predominantly comedonal acne, are now considered first-line treatment for both comedonal and inflammatory acne. By inhibiting microcomedone formation, retinoids prevent the formation of new lesions; thus, these agents are now considered an essential part of maintenance therapy. Taken together, these effects of retinoids can help to break the cycle of acne.

For best results, topical retinoids should be initiated at the onset of therapy and applied to the entire affected area.[3] Topical retinoids can cause some burning and irritation in some patients, especially in the early weeks of therapy. Identifying patients who are more likely to experience this generally manageable adverse effect can improve compliance; therefore, all patients should be asked about their skin care regimens at their initial visit. Important information includes which cleansers they use daily, whether they are or have used any over-the-counter acne medications (if so, did they tolerate them?), and whether they feel they have sensitive skin. With this information in mind, clinicians can choose the best retinoid for patients. When selecting a retinoid, the vehicle must be considered, because certain retinoids are associated with more irritation than others. For instance, alcohol-based gels are generally more irritating than a cream-based product.[23] Educating the patient with tips for retinoid use can also help to increase tolerance. By starting off with a reduced frequency of application (every second or third day) and shorter duration of contact (washing off the application after a period of time), improved tolerance should be achieved. Patients may exacerbate irritation by using more of the medication than is necessary for efficacy. A pea-sized amount is sufficient; it should be divided into 4 equal aliquots and smoothed over the entire surface of the face. Retinoids should not be used as a spot therapy. Make sure patients are not using any over-the-counter medications such as salicylic acid scrubs or astringents without your knowledge. Use of these products while starting a retinoid may increase irritancy.

Mechanism of Action

Topical retinoids regulate the follicular keratinocyte. They normalize keratinocyte desquamation by affecting follicular epithelial turnover and cell maturation.[24,25] Topical retinoids also have direct antiinflammatory properties, affecting the immune response, inflammatory cell migration, and inflammatory mediators.[26,27] A topical retinoid has been shown to decrease free fatty acid levels in the microcomedo, similar to the effect seen with antibiotic therapy, supporting an antiinflammatory role.[25,26]

Because retinoids inhibit the formation of the microcomedo, they prevent the formation of both comedones and inflammatory lesions.[28,29] In fact, as shown in a 12-week, multicenter, randomized, investigator-blinded study conducted by Shalita et al,[29] topical retinoid monotherapy has a potent effect on inflammatory lesions, which is comparable to the effect on comedones (Fig 6). Finally, given their effects on keratinization, topical retinoids enhance penetration of topical antibiotics and BPO.[3,24,30,31] As a result, topical retinoids effectively diminish microcomedo formation, reduce existing noninflammatory and inflammatory lesions, and lessen the formation of new lesions.[3]

Results of Clinical Trials

Several topical retinoids are currently approved for use in the United States: tretinoin, adapalene, and tazarotene. Despite differences in their chemical structure,

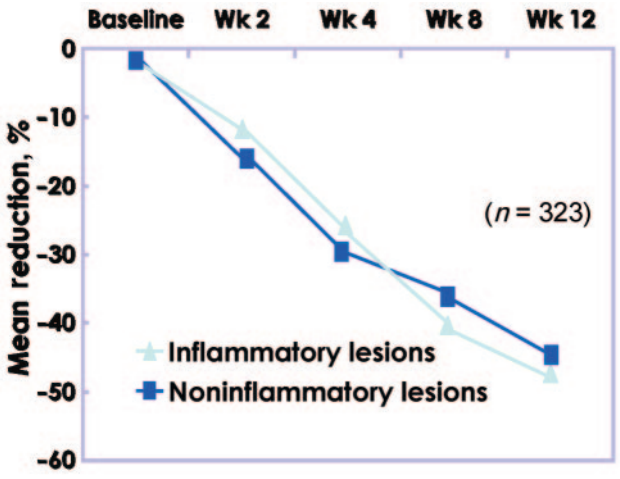

FIGURE 6
Effect of topical retinoids (adapalene) on inflammatory and noninflammatory lesions. (Adapted from Shalita A, Weiss JS, Chalker DK, et al. *J Am Acad Dermatol*. 1996;34:482–485.)

they all decrease formation of microcomedos and subsequent acne lesions. All have demonstrated efficacy in clinical studies; the primary distinguishing factor is cutaneous tolerability, which can vary between formulations.

Tretinoin was the first commercially available retinoid in the United States. In 12-week clinical trials, reductions were observed in both comedones (33%–81%) and inflammatory lesions (17%–71%).[3] In vehicle-controlled studies, all acne lesions were reduced by up to 50% in patients treated with once-daily tretinoin therapy.[32,33] Tretinoin is available in various formulations and strengths (Table 2). Generally, it should be started at a low strength and increased as needed to minimize the potential for irritation. Patients with atopic dermatitis, rosacea, and other skin conditions that cause sensitive skin may be especially prone to irritation with topical tretinoin therapy.[3] Compatibility studies have shown that tretinoin's chemical stability is affected by light and degrades to a greater extent when administered concomitantly with BPO[34]; therefore, BPO should be used in the morning and tretinoin should be applied at night to ensure greatest efficacy.

TABLE 2 **Available Formulations of Topical Retinoids**

Retinoid	Formulation	Strength, %
Tretinoin	Cream	0.025, 0.05, 0.1
	Gel	0.01, 0.025
	Liquid	0.05
	Microsphere gel (Retin-A Micro)	0.04, 0.1
	Polymerized cream (Avita)	0.025
	Polymerized gel (Avita)	0.025
Adapalene (Differin)	Cream	0.1
	Gel	0.1
	Solution	0.1
Tazarotene (Tazorac)	Cream	0.05,[a] 0.1
	Gel	0.05,[a] 0.1

[a] Indicated for psoriasis.

In response to the problems of cutaneous irritation (eg, erythema, desquamation, burning, pruritus) that were observed with the original formulations of tretinoin, 2 newer formulations were developed: tretinoin microsphere and polymerized tretinoin. Retin-A Micro (0.1% gel and 0.04% gel; OrthoNeutrogena, Skillman, NJ) is composed of porous copolymer microspheres that slowly release tretinoin into the sebaceous follicle. Studies directly comparing Retin-A Micro to the original tretinoin formulation (Retin-A; OrthoNeutrogena) have not been conducted, but results of vehicle-controlled studies were consistent with those of other tretinoin formulations.[35] The polymerized tretinoin formulation (Avita 0.025% cream and 0.025% gel; Mylan Pharmaceuticals, Morgantown, WV) uses a unique polyolprepolymer-2 vehicle to release tretinoin in a slow, controlled-release fashion. The safety and efficacy of polymerized tretinoin are comparable to tretinoin cream and gel.[3,33,35]

Adapalene, a naphthoic acid derivative with retinoid activity, is available as a gel, solution, and cream.[3] The efficacy and tolerability of adapalene have been established in numerous controlled clinical studies.[29,36–45] For example, in a meta-analysis of 5 large, well-controlled, comparative studies in which >900 patients were evaluated, efficacy with adapalene gel 0.1% was similar to that with tretinoin gel 0.025%.[46] Adapalene-treated patients experienced a 49% to 63% mean reduction of lesions over 12 weeks, with the majority (80%–89%) achieving a favorable clinical response.[3] Adapalene is also similar to tretinoin microsphere in terms of efficacy[45] while exhibiting greater tolerability than tretinoin and tretinoin microsphere.[45,46]

Adapalene was designed specifically for acne; it has molecular characteristics that allow it to specifically penetrate the pilosebaceous unit. In addition, it is very well tolerated. Studies comparing the potential for cutaneous irritation among topical retinoids have consistently shown that the adapalene molecule is the best tolerated of the available retinoids (Fig 7).[47] In fact, adapalene is almost as well tolerated as the control agent used in studies of cutaneous irritation.[40] In addition, adapalene is both photostable and remains stable with concomitant BPO use.[34]

Tazarotene, currently available in the United States in 0.05% and 0.1% gel or cream formulations (0.1% concentration is approved for treatment of acne), also has been shown effective in well-controlled clinical trials.[3,48,49] In a double-blind, multicenter study in which patients with acne were randomly assigned to receive vehicle, tazarotene 0.05%, or tazarotene 0.1% once daily, clinical success (rated as excellent or good by the investigator, >50% improvement) was observed in 40%, 51%, and 68% of patients, respectively.[49] Compar-

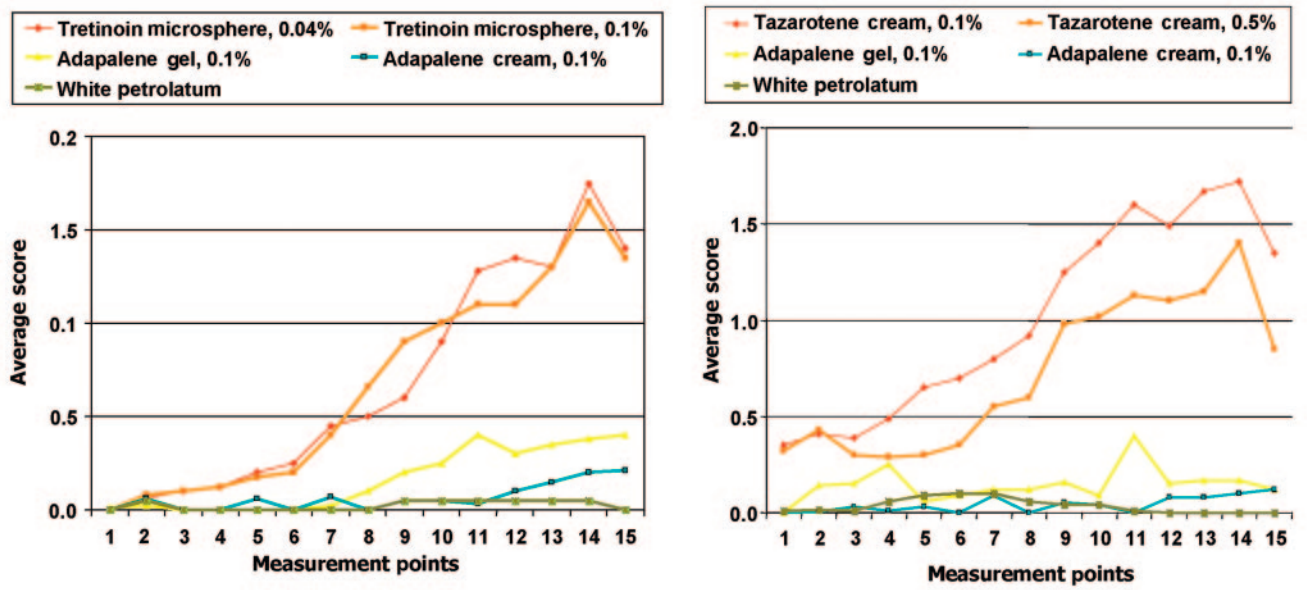

FIGURE 7
Tolerability of topical retinoids: 21-day cumulative irritancy study in healthy volunteers. (Data on file, Galderma Laboratories, LP.)

ative studies suggest that tazarotene may be more effective than tretinoin or adapalene in reducing papules and open comedones, with equal efficacy against closed comedones.[50,51] However, many patients experience retinoid dermatitis when tazarotene is used on a daily basis. For this reason, investigators have evaluated every-other-day and short-contact (application for short periods of time followed by removal) application strategies; both have been shown to improve acne.[50] Tazarotene also is stable when exposed to ultraviolet light.

Of note, epidemiologic and pharmacokinetic studies do not support an association of topical retinoids with birth defects.[52,53] However, there have been case reports of birth defects occurring in infants of mothers who used topical retinoids during pregnancy.[54] For this reason, they are not recommended for use during pregnancy or breastfeeding. Tretinoin and adapalene carry a pregnancy category C rating and should be used with appropriate caution in women and adolescents of childbearing age. Tazarotene has a pregnancy category X rating and is contraindicated during pregnancy.

Combination Therapy: Appropriate for Most Patients With Acne

Because multiple factors are involved in the development of acne, experts stress the importance of combination treatment to target as many pathophysiologic factors of acne as possible.[3] The beneficial effects of combining acne agents include targeting different pathophysiologic factors (ie, abnormal desquamation, *P acnes* proliferation, and inflammation), increasing efficacy, improving the speed of lesion resolution, and minimizing the potential for antibiotic resistance.

Combination therapy, including a topical retinoid with either a topical or oral antibiotic and BPO, is now considered the standard of care for patients with both comedonal and inflammatory acne. Clinical studies have consistently shown faster and better clearing of both inflammatory lesions and comedones with such a combination when compared with antimicrobial therapy alone.[3]

More than 25 years ago, Mills and Kligman[31] compared the efficacy of topically applied tretinoin 0.05% solution and erythromycin 2% solution to that of retinoid, antibiotic, or vehicle alone in patients with moderately severe acne. A clinical-effectiveness rating of excellent (≥75% reduction in lesion count) or good (50%–74% reduction) was observed in 75% of the patients treated with combination therapy, 50% treated with tretinoin, 45% with erythromycin, and 10% with vehicle. Since that time, numerous studies have shown similar results. For example, in a comparison of topical clindamycin 0.1% plus tretinoin 0.025% gel versus clindamycin alone, Zouboulis et al[55] reported faster improvement and greater reductions in both noninflammatory ($P = .05$) and inflammatory ($P = .018$) lesions after 12 weeks of therapy. More recently, the combination of 0.1% adapalene gel and 1% topical clindamycin lotion was evaluated in a multicenter, randomized, investigator-blinded 12-week study of 249 patients with mild-to-moderate acne.[56] A significantly greater reduction in acne lesions was observed in the combination-therapy group as compared with the topical-antibiotic group by week 2, with the difference between treatment groups steadily increasing to the study's end (Fig 8).[56]

Faster and greater improvement also has been re-

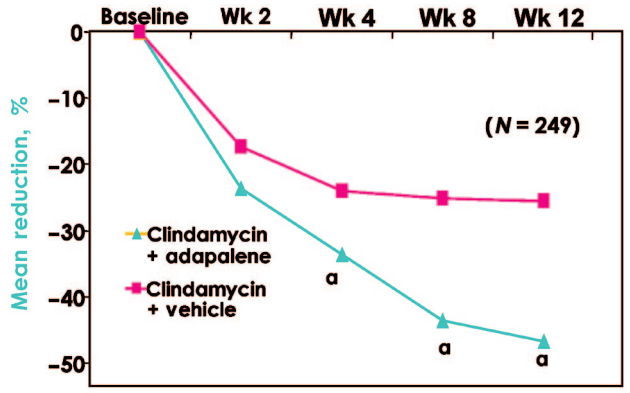

FIGURE 8
Topical retinoid plus antibiotic versus topical antibiotic alone. [a] $P \leq .001$. (Adapted from Wolf JE, Kaplan D, Kraus SJ, et al. *J Am Acad Dermatol*. 2003;49[3 suppl]:S211–S217.)

ported in studies comparing the combination of a retinoid and oral antibiotic with an oral antibiotic alone. For instance, in a multicenter, investigator-blinded study, Thiboutot et al[57] randomly assigned 467 patients with moderate to moderately severe inflammatory acne to receive 0.1% adapalene gel plus doxycycline hyclate (100 mg/day) or the antibiotic alone plus adapalene gel vehicle. The reduction in lesions was significantly greater in those in the combination arm compared with those in the antibiotic-monotherapy arm (−61.2% vs −45.3%, respectively; $P < .005$). In addition, differences between groups were apparent as early as week 4 (Fig 9).[57] Notably, neither local tolerability nor adverse events were significantly different between groups. Patient reports of satisfaction with treatment effectiveness were markedly greater in the combination arm versus

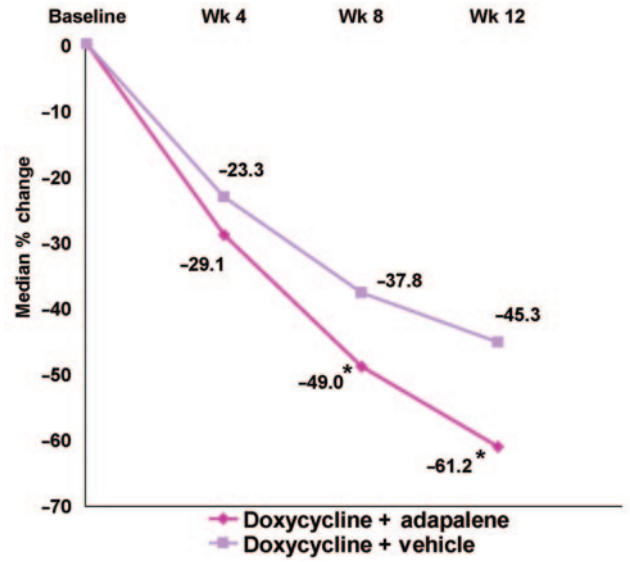

FIGURE 9
Topical retinoid plus oral antibiotic versus oral antibiotic alone. [a] $P \leq .005$. (Adapted from Thiboutot DM, Shalita AR, Yamauchi PS, et al. *Skinmed*. 2005;4:138–146.)

the antibiotic-monotherapy arm (78% vs 64%, respectively).[57]

There are no head-to-head comparisons of doxycycline 100 mg/day versus 200 mg/day, nor are there such comparisons for minocycline. Comparative clinical trial data are also absent on tissue levels of doxycycline or minocycline when using the same daily dose in a person weighing 45 kg versus a person weighing 90 kg. Nevertheless, despite recommended dosing of doxycycline 100 mg/day for many infections, the 200 mg/day regimen is often used in clinical practice for the treatment of acne.

Antimicrobials: Use in Patients With Inflammatory Lesions

First introduced in the 1930s and 1940s, antibiotics have long been considered a mainstay in the treatment of acne vulgaris. Now, however, acne experts are recommending that antibiotics play an adjunctive, rather than primary, role in acne treatment.[3]

In this climate of increasing antibiotic resistance, a recent study in the United Kingdom attempted to compare antimicrobial regimens for efficacy and cost-effectiveness in the treatment of mild-to-moderate inflammatory facial acne.[58] Study participants were randomly assigned to 1 of 5 regimens: oral oxytetracycline and topical placebo; oral minocycline and topical placebo; oral placebo and topical BPO; oral placebo and Benzamycin (BPO plus 3% erythromycin; Sanofi-Aventis, Bridgewater, NJ); or oral placebo and topical erythromycin in the morning plus topical BPO in the evening. The regimen comprising minocycline alone was found to be the one most compromised by antibiotic resistance. Study results showed that topical BPO alone and topical BPO/erythromycin combinations were similar in efficacy to the oral antibiotic regimens and were not affected by propionibacterial antibiotic resistance. The authors admitted to study limitations in low recruitment rate and the absence of participant masking. Furthermore, these regimens did not include comparisons or combinations with topical retinoids, and generalization from a study of those with mild-to-moderate acne to those with severe disease may be inappropriate. Nonetheless, the study does highlight the well-established concept that antibiotic therapy alone is not effective in treating acne.

With this in mind, antibiotic agents should not be used as monotherapy, because combination therapy with topical retinoids will provide faster and greater results and, therefore, will help prevent antibiotic resistance. Oral antibiotic therapy should be reserved for patients with moderate-to-severe inflammatory acne.[25,59] Typically, tetracycline and the tetracycline derivatives are used; alternate choices include macrolides, co-trimoxazole, and trimethoprim.[59] The topical macrolides, erythromycin and clindamycin, may be used alone or in combination with BPO, a highly effective and readily available antimicrobial in itself. Indeed, formula-

tions that combine clindamycin and BPO are currently very popular in the management of acne.[3]

Topical Antibiotics

Topical antibiotics are indicated for mild inflammatory acne. These medicines are typically very well tolerated apart from occasional mild cutaneous irritation and burning. Topical clindamycin therapy has been very rarely associated with pseudomembranous colitis.[60] Unfortunately, antibiotic resistance is fairly common, especially with prolonged use of the topical antibiotics without concomitant use of BPO.[3] Again, it is for this reason that topical antibiotics are no longer recommended as monotherapy for acne.

BPO

BPO is the most potent topical antimicrobial with rapid bactericidal action, resulting in a rapid reduction in bacterial organisms.[61,62] Microorganisms, including *P acnes*, are unable to develop resistance to BPO[62,63]; combining a topical antibiotic with BPO reduces the development of resistant strains of *P acnes* and allows longer duration of therapy.[64] In addition, combination therapies that use an antibiotic with BPO are more effective with less irritation than BPO used alone.[65] However, used alone, BPO can significantly improve inflammatory acne.

BPO is widely available in many different formulations including soaps, washes, creams, gels, and lotions. It comes in concentrations of 1% to 10%. Studies have shown that even at lower concentrations, such as 2.5%, BPO is an effective antimicrobial.[65,66] Skin type and distribution of inflammatory lesions will help to determine which formulation of BPO is chosen.[67] For patients with sensitive skin, a lower strength in a cream or lotion may be preferred. If there is significant chest and back involvement, a BPO wash is an excellent choice for convenience of application and improved compliance.[3]

Skin irritation is the most common adverse effect with the use of BPO. The irritation depends on concentration and formulation; it is typically worse during the first few days of therapy and generally improves with time. It is also important to warn patients that BPO can bleach color out of clothing, bedding, and even hair.[3]

Oral Antibiotics

For most cases of moderate-to-severe acne, oral antibiotic therapy should be instituted along with a topical retinoid and BPO. Tetracycline and its second-generation derivatives, doxycycline and minocycline, are the standard first-line choice of antibiotic in most cases.[59] However, according to estimates, 1 in 4 patients with acne may have strains of *P acnes* that are resistant to tetracycline, erythromycin, and clindamycin.[68] Bacterial resistance has made the use of oral erythromycin in the treatment of acne uncommon.[69,70] Its use should be reserved for children without their permanent dentition, pregnant women, and those with a hypersensitivity to tetracyclines.[3,67]

Oral antibiotics work primarily through the reduction of resident skin bacteria, *P acnes* and *Staphylococcus epidermidis*.[59] In addition to their antimicrobial properties, antibiotics also have intrinsic antiinflammatory properties, exerting their action through the inhibition of neutrophil chemotaxis and alteration of macrophage and cytokine production.[3,59,71–74] The tetracyclines also have been shown to increase local prostaglandin synthesis while inhibiting nitric-oxide synthetase.[3] Both minocycline and doxycycline can inhibit granulomatous inflammation, and minocycline also has been shown to increase superoxide dismutase, an enzyme.[3]

Dosing depends on the antibiotic prescribed. Tetracycline is typically started at an oral dose of 500 mg twice per day. It is important to instruct patients that tetracycline must be taken 1 hour before or 2 hours after meals to ensure adequate absorption. The standard starting dose for minocycline and doxycycline is 100 to 200 mg daily. Once improvement is noted, the oral antibiotic should be discontinued as soon as possible.[75] If no improvement is seen, a change in antibiotic is warranted, because resistance is not uncommon. Once off of oral therapy, patients should continue with topical retinoid therapy to maintain improvement.

Oral antibiotic therapy in the treatment of moderate-to-severe inflammatory acne is typically well tolerated in most patients.[76] Common (>1% incidence) and uncommon (<1% incidence) adverse effects are listed in Table 3.[63,75,77,78] It is important to note that tetracycline and its derivatives should not be used in pregnant females or children younger than 10 years.[3,75] Permanent discoloration of the teeth and abnormal skeletal development are potential consequences of using tetracyclines in children before complete calcification of bones and teeth.[3,79]

Of note to women of childbearing age is the concern that concurrent use of antibiotics and oral contraceptives

TABLE 3 **Oral Antibiotic adverse Effects**

Class	Antibiotic	Common Adverse Effects	Uncommon Adverse Effects
Tetracyclines	Tetracycline	Candidiasis	
	Doxycycline	Photosensitivity	
	Minocycline	Candidiasis	*Pseudotumor cerebri*, blue-gray hyperpigmentation, drug-induced lupus[63,75,77,78]
Macrolides	Erythromycin	Gastrointestinal upset, candidiasis	

could reduce contraceptive efficacy. There are few studies to address the issue, because it is difficult to define; however, in practice, it is advisable to discuss the potential risk with patients.

Antimicrobial Resistance

As with the treatment of infectious diseases, antibiotic resistance in the treatment of acne is of increasing concern. In the 1970s, resistant strains of *P acnes* were virtually nonexistent.[68,70,80] By the late 1980s, resistance was beginning to emerge and has been rising steadily since.[3,68] Increased use of topical antibiotics is credited for this change. Especially important is that resistant strains of *P acnes* also can be disseminated among close contacts.[70]

Resistance should be suspected in patients who do not respond within 8 to 16 weeks of initiation of antibiotic therapy. If this occurs, the antibiotic should be discontinued and an alternate antibiotic chosen. Tetracycline, doxycycline, and minocycline have been mentioned previously. Additional antibiotics commonly used for the treatment of acne in specific instances include lymecycline (150–300 mg daily before meals) for use outside of the United States; erythromycin (333 mg 3 times daily with meals) for children under the age of 12 years, in whom staining of emerging dentition is a consideration; and for patients who are allergic or unresponsive to aminoglycosides and tetracyclines, trimethoprim/sulfamethoxazole as 2 tablets daily (800 mg of sulfamethoxazole and 160 mg of trimethoprim) and trimethoprim 300 mg twice a day.[3] Because of the lack of efficacy and safety considerations in treating acne, cephalosporins, fluoroquinolones, aminoglycosides, chloramphenicol, sulfonamides/sulfur, and gyrase inhibitors are not recommended for routine use.

Although *P acnes* resistance is the most likely suspect in nonresponders, it is worth noting that organisms such as *Staphylococcus aureus*, Gram-negative bacteria, and *Pityrosporum* species have been known to occasionally play a secondary role in recalcitrance to standard antibiotic therapies. Pityrosporum folliculitis, for example, will often worsen with antibiotic therapy and respond to antifungal therapy, whereas Gram-negative organisms can flourish in patients with long-term tetracycline use.

Limiting the use of antibiotics and avoiding their long-term use minimizes the development of microbial resistance. Once improvement is noted, the antibiotic should be discontinued and maintenance therapy instituted. Recurrent courses may be necessary for flare-ups. For topical therapy, combination therapy using an antibiotic with BPO can inhibit the development of resistance (Table 4).

TABLE 4 Guidelines for Oral Antibiotic Use

For moderate-to-severe inflammatory acne
Avoid antibiotic monotherapy
Combine with a topical retinoid
Add BPO to reduce resistance
Treat for at least 6–8 wk for minimum improvement
Reevaluate need for antibiotic at 12–18 wk
Use the same antibiotic if additional courses are required
If antibiotic treatment is ineffective, try another antibiotic
Encourage compliance with regimen
Add hormonal therapy for selected females

Other Therapies

Hormonal therapy, namely oral contraceptives and spironolactone, may be a good option for managing acne in females who have sudden onset of severe acne, who have not responded to conventional first-line therapy, or who have persistent inflammatory papules and nodules involving primarily the lower face and neck.[3] Hormonal therapies are also integral to treating female patients with hyperandrogenism (hirsutism, androgenetic alopecia, deepening of the voice).[3] Hormonal therapy is especially beneficial in patients who have additional reasons for oral contraceptive use, such as birth control or regulation of irregular menstrual cycles.[3] It should be noted that, according to prescribing guidelines, the vast majority of female patients of childbearing potential with severe nodular acne will need concomitant use of an oral contraceptive (or other highly effective form of birth control) before starting isotretinoin therapy.

Maintenance Therapy

Once clinical improvement is achieved, a change to maintenance therapy should be initiated, particularly in the young teenager whose acne is likely to recur. On the basis of its mechanism of action, a topical retinoid should be continued; formation of microcomedones begins immediately after discontinuation of retinoid therapy. Clinical data also support this approach. Patients who participated in a 12-week study, in which 0.1% adapalene gel plus oral doxycycline and oral antibiotic plus adapalene vehicle were compared, then entered a 16-week extension study. The total number of lesions increased among patients who applied only vehicle and remained stable in those who continued applying adapalene gel (Fig 10).[81] These data underscore the fact that maintenance therapy with a topical retinoid is important in acne, because the disease tends to recur without an ongoing treatment regimen.[47]

Although maintaining retinoid therapy is recommended, oral and topical antibiotic therapy (discussed below) should be discontinued immediately after inflammatory lesions are under good control.[3] If continued antimicrobial therapy is needed, BPO can be used in combination with the topical retinoid.

Patient Management Strategies

Because having acne can have a major impact on a teenager's quality of life, asking patients how they feel

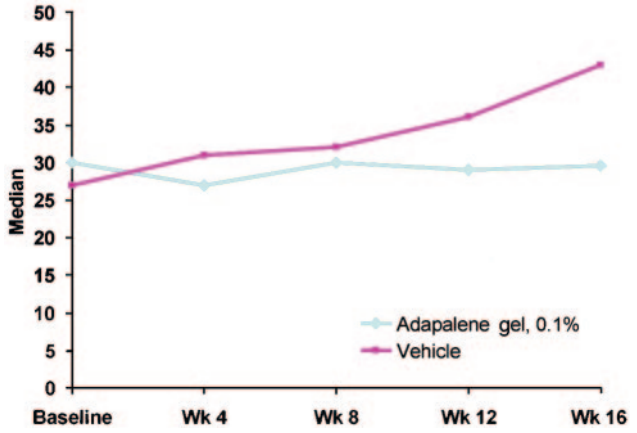

FIGURE 10
Impact of maintenance therapy on acne lesions after good control has been achieved. [a] $P \leq .0011$. (Adapted from Thiboutot D, Pariser DM, Egan N, et al. *J Am Acad Dermatol*. 2006;54:242–250.

about their acne and what expectations they have from treatment at baseline provides a foundation for assessing improvement during the course of therapy. Understanding this relationship can help clinicians develop strategies to improve treatment compliance. Patient education is essential. The patient is well served by physicians who dispel the myths surrounding acne and provide accurate information about how acne develops. Drinking soda or eating chocolate does not cause acne,[3,80] nor is acne the result of being unclean, and it cannot be washed or scrubbed away.[3,80]

At the initial visit, patients should be given realistic goals of therapy; they should be informed that, although good therapy options are available, treatment takes time (≥4–8 weeks) before improvement is noticeable.[29,82] Patients need to be advised that acne may appear to worsen in the early weeks of therapy, but tolerance strategies will lessen the potential irritation. In addition, clear, written instructions about the application of medications and general skin care (eg, using only the hands for facial washing; using a mild synthetic cleanser) should be provided to all patients starting acne treatment. At follow-up visits, patients' daily skin care routine should be reviewed: When are they using their medications and to which areas? What cleansers are they using? Are they moisturizing and/or using sunblock? Patients should be asked to assess the progress of their treatment, and any concerns they have should be addressed, with an emphasis on the need for patience and persistence. In patients for whom compliance is an issue, they should be asked what can make the regimen more effective. For example, if the patient showers at night and has been instructed to use a BPO wash in the shower, using a retinoid incompatible with a BPO will compromise the efficacy of the regimen. Also, if a patient cannot tolerate, or his or her schedule does not allow time for, tetracycline on an empty stomach, doxycycline or minocycline may be a better choice. Finally, once improvement is achieved, the importance of maintenance therapy should be discussed, because acne tends to recur without an ongoing treatment regimen.

CONCLUSIONS

Targeting multiple pathophysiologic factors is an effective strategy for managing acne. For this reason, combination therapy involving a topical retinoid and antimicrobial is recommended as first-line treatment for the majority of patients. The newer generation of topical retinoids is well tolerated and easy to use. Their ability to inhibit microcomedo formation also makes them an essential part of maintenance therapy. Antibiotics are more effective when used in combination therapy and should be discontinued once inflammatory lesions are adequately cleared. Antibiotic resistance in the treatment of acne is of increasing concern, and the use of BPO with antibiotics can inhibit the development of resistance. Perhaps the most important tool in the effective management of acne concerns the clinician's ability to educate and listen to the patient, working together to provide the best treatment strategy for that individual. Doing so will ensure better compliance and, thus, better outcomes.

MEMBERS OF GLOBAL ALLIANCE TO IMPROVE OUTCOMES IN ACNE

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REFERENCES

1. Leyden JJ. New understandings of the pathogenesis of acne. *J Am Acad Dermatol.* 1995;32:S15–S25
2. Cunliffe WJ, Gould DJ. Prevalence of facial acne vulgaris in late adolescence and in adults. *Br Med J.* 1979;1(6171):1109–1110
3. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2003;49(1 suppl):S1–S37
4. Pochi PE, Strauss JS, Downing DT. Age-related changes in sebaceous gland activity. *J Invest Dermatol.* 1979;73:108–111
5. Pochi PE, Strauss JS. Endocrinologic control of the development and activity of the human sebaceous gland. *J Invest Dermatol.* 1974;62:191–201
6. Gollnick HPM, Zouboulis CC, Akamatsu H, Kurokawa I, Schulte A. Pathogenesis and pathogenesis related treatment of acne. *J Dermatol.* 1991;18:489–499
7. Thiboutot D, Harris G, Iles V, Cimis G, Gilliland K, Hagari S. Activity of the type 1 5-α-reductase exhibits regional differences in isolated sebaceous glands and whole skin. *J Invest Dermatol.* 1995;105:209–214

8. Thiboutot D, Knaggs H, Gilliland H, Lin G. Activity of 5-alpha-reductase and 17-beta-hydroxysteroid dehydrogenase in the infrainfundibulum of subjects with and without acne vulgaris. *Dermatology.* 1998;196:38–42
9. Thiboutot DM, Knaggs H, Gilliland K, Hagari S. Activity of type 1 5α-reductase is greater in the follicular infrainfundibulum compared with the epidermis. *Br J Dermatol.* 1997;136:166–171
10. Chen W, Zouboulis CC, Fritsch M, Kodelja V, Orfanos CE. Heterogeneity and quantitative differences of type 1 5α-reductase expression in cultured skin epithelial cells. *Dermatology.* 1998;196:51–52
11. Fritsch M, Orfanos CE, Zouboulis CC. Sebocytes are the key regulators of androgen homeostasis in human skin. *J Invest Dermatol.* 2001;116:793–800
12. Schmidt JB, Spona J, Huber J. Androgen receptor in hirsutism and acne. *Gynecol Obstet Invest.* 1986;22:206–211
13. Holmes RL, Williams M, Cunliffe WJ. Pilo-sebaceous duct obstruction and acne. *Br J Dermatol.* 1972;87:327–332
14. Plewig G, Fulton JE, Kligman AM. Cellular dynamics of comedo formation in acne vulgaris. *Arch Dermatol Forsch.* 1971;242:12–29
15. Kurokawa I, Mayer-da-Silva A, Gollnick H, Orfanos CE. Occurrence and distribution of cytokeratins and filaggrin in the human pilosebaceous unit: an immunocytochemical study. In: Marks R, Plewig G, eds. *Acne and Related Disorders*. London, England: Martin Dunitz; 1989:19–22
16. Cunliffe WJ, Holland DB, Clark SM, Stables GI. Comedogenesis: some new aetiological, clinical and therapeutic strategies. *Br J Dermatol.* 2000;142:1084–1091
17. Leyden JJ, McGinley KJ, Mills OH, Kligman AM. Propionibacterium levels in patients with and without acne vulgaris. *J Invest Dermatol.* 1975;65:382–384
18. Norris JF, Cunliffe WJ. A histological and immunocytochemical study of early acne lesions. *Br J Dermatol.* 1988;118:651–659
19. Toyoda M, Morohashi M. Pathogenesis of acne. *Med Electron Microsc.* 2001;34:29–40
20. Puhvel SM, Sakamoto M. The chemoattractant properties of comedonal components. *J Invest Dermatol.* 1978;71:324–329
21. Cunliffe WJ. The sebaceous gland and acne: 40 years on. *Dermatology.* 1998;196:9–15
22. Leyden JJ. Therapy for acne vulgaris. *N Engl J Med.* 1997;336:1156–1162
23. Draelos ZK. Patient compliance: enhancing clinician abilities and strategies. *J Am Acad Dermatol.* 1995;32:S42–S48
24. Gollnick H, Schramm M. Topical drug treatment in acne. *Dermatology.* 1998;196:119–125
25. Thielitz A, Helmdach M, Röpke EM, Gollnick H. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying therapeutic effects of antiacne agents. *Br J Dermatol.* 2001;145:19–27
26. Verschoore M, Bouclier M, Czernielewski J, Hensby C. Topical retinoids: their uses in dermatology. *Dermatol Clin.* 1993;11:107–115
27. Hensby C, Cavey D, Bouclier M, et al. The in vivo and in vitro anti-inflammatory activity of CD271: a new retinoid-like modulator of cell differentiation. *Agents Actions.* 1990;29:56–58
28. Kligman AM, Fulton JE Jr, Plewig G. Topical vitamin A acid in acne vulgaris. *Arch Dermatol.* 1969;99:469–476
29. Shalita A, Weiss JS, Chalker DK, et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. *J Am Acad Dermatol.* 1996;34:482–485
30. Gollnick H, Schramm M. Topical therapy in acne. *J Eur Acad Dermatol Venereol.* 1998;11(suppl 1):S8–S12; discussion S28–S29
31. Mills OH Jr, Kligman AM. Treatment of acne vulgaris with topically applied erythromycin and tretinoin. *Acta Derm Venereol.* 1978;58:555–557
32. Lucky AW, Cullen SI, Funicella T, Jarratt MT, Jones T, Reddick ME. Double-blind, vehicle-controlled multicenter comparison of two 0.025% tretinoin creams in patients with acne vulgaris. *J Am Acad Dermatol.* 1998;38:S24–S30
33. Lucky AW, Cullen SI, Jarratt MT, Quigley JW. Comparative efficacy and safety of two 0.025% tretinoin gels: results from a multicenter, double-blind, parallel study. *J Am Acad Dermatol.* 1998;38:S17–S23
34. Martin B, Meunier C, Montels D, Watts O. Chemical stability of adapalene and tretinoin when combined with benzoyl peroxide in presence and in absence of visible light and ultraviolet radiation. *Br J Dermatol.* 1998;139(suppl 52):8–11
35. Retin-A [package insert: full prescribing information]. Skillman, NJ: Ortho Dermatological; 2002
36. Dunlap FE, Mills OH, Tuley MR, Baker MD, Plott RT. Adapalene 0.1% gel for the treatment of acne vulgaris: its superiority compared to tretinoin 0.025% cream in skin tolerance and patient preference. *Br J Dermatol.* 1998;139(suppl 2):17–22
37. Weiss JS, Shavin JS. Adapalene for the treatment of acne vulgaris. *J Am Acad Dermatol.* 1998;39:S50–S54
38. Caron D, Sorba V, Kerrouche N, Clucas A. Split-face comparison of adapalene 0.1% gel and tretinoin 0.025% gel in acne patients. *J Am Acad Dermatol.* 1997;36:S110–S112
39. Millikan LE. Adapalene: an update on newer comparative studies between the various retinoids. *Int J Dermatol.* 2000;39:784–788
40. Clucas A, Verschoore M, Sorba V, Poncet M, Baker M, Czernielewski J. Adapalene 0.1% gel is better tolerated than tretinoin 0.025% gel in acne patients *J Am Acad Dermatol.* 1997;36:S116–S118
41. Cunliffe WJ, Caputo R, Dreno B, et al. Clinical efficacy and safety comparison of adapalene gel and tretinoin gel in the treatment of acne vulgaris: Europe and U.S. multicenter trials. *J Am Acad Dermatol.* 1997;36(suppl 2):S126–S134
42. Piérard-Franchimont C, Henry F, Fraiture AL, Fumal I, Piérard GE. Split-face clinical and bio-instrumental comparison of 0.1% adapalene and 0.05% tretinoin in facial acne. *Dermatology.* 1999;198:218–222
43. Galvin SA, Gilbert R, Baker M, Guibal F, Tuley MR. Comparative tolerance of adapalene 0.1% gel and six different tretinoin formulations. *Br J Dermatol.* 1998;139(suppl 52):34–40
44. Grosshans E, Marks R, Mascaro JM, et al. Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life. *Br J Dermatol.* 1998;139(suppl 52):26–33
45. Wolf JE. An update of recent clinical trials examining adapalene and acne. *J Eur Acad Dermatol Venereol.* 2001;15(suppl 3):23–29
46. Cunliffe WJ, Poncet M, Loesche C, Verschoore M. A comparison of the efficacy and tolerability of adapalene 0.1% gel versus tretinoin 0.025% gel in patients with acne vulgaris: a meta-analysis of five randomized trials. *Br J Dermatol.* 139(suppl 52):48–56, 1998
47. Thielitz A, Helmdach M, Rapke EM, Gollnick H. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying therapeutic effects of antiacne agents. *Brit J Dermatol.* 2001;145:19–27
48. Russell JJ. Topical therapy for acne. *Am Fam Physician.* 2000;61:357–365
49. Shalita AR, Chalker DK, Griffith RF, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. *Cutis.* 1999;63:349–354
50. Bershad S. Topical retinoids in the treatment of acne vulgaris. *Cutis.* 1999;64(suppl 2):8–23

51. Kakita L. Tazarotene versus tretinoin or adapalene in the treatment of acne vulgaris. *J Am Acad Dermatol.* 2000;43:S51–S54
52. Loureiro KD, Kao KK, Jones KL, et al. Minor malformations characteristic of the retinoic acid embryopathy and other birth outcomes in children of women exposed to topical tretinoin during early pregnancy. *Am J Med Genet A.* 2005;136:117–121
53. Jick SS, Terris BZ, Jick H. First trimester topical tretinoin and congenital disorders. *Lancet.* 1993;341:1181–1182
54. Selcen D, Seidman S, Nigro MA. Otocerebral anomalies associated with topical tretinoin use. *Brain Dev.* 2000;22:218–220
55. Zouboulis CC, Derumeaux L, Decroix J, Mariejewska-Udziela B, Cambazard F, Stuhlert A. A multicentre, single-blind, randomized comparison of a fixed clindamycin phosphate/tretinoin gel formulation (Velac) applied once daily and a clindamycin lotion formulation (Dalacin T) applied twice daily in the topical treatment of acne vulgaris. *Br J Dermatol.* 2000;143:498–505
56. Wolf JE, Kaplan D, Kraus SJ, et al. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blinded study. *J Am Acad Dermatol.* 2003;49(3 suppl):S211–S217
57. Thiboutot DM, Shalita AR, Yamauchi PS, et al. Combination therapy with adapalene gel 0.1% and doxycycline for severe acne vulgaris: a multicenter, investigator-blind, randomized, controlled study. *Skinmed.* 2005;4:138–146
58. Ozolins M, Eady EA, Avery AJ, et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. *Lancet.* 2004;364:2188–2195
59. Meynadier J, Guillot B. Trétinoïne-érythromycine base: leur activité anti-inflammatoire. *Gaz Med France.* 1983;90:2551–2554
60. Parry MF, Rha C-K. Pseudomembranous colitis caused by topical clindamycin phosphate. *Arch Dermatol.* 1986;122:583–584
61. Kligman AM, Mills OH, McGinley KJ, Leyden JJ. Acne therapy with tretinoin in combination with antibiotics. *Acta Derm Venereol Suppl (Stockh).* 1975;74:111–115
62. White GM. Acne therapy. *Adv Dermatol.* 1999;14:29–58; discussion 59
63. Bojar RA, Cunliffe WJ, Holland KT. The short-term treatment of acne vulgaris with benzoyl peroxide: effects on the surface and follicular cutaneous microflora. *Br J Dermatol.* 1995;132:204–208
64. Eady EA, Bojar RA, Jones CE, Cove JH, Holland KT, Cunliffe WJ. The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. *Br J Dermatol.* 1996;134:107–113
65. Leyden JJ, Shalita AR. Rational therapy for acne vulgaris: an update on topical treatment. *J Am Acad Dermatol.* 1986;15:907–915
66. Kligman AM. Acne vulgaris: tricks and treatments. Part II: The benzoyl peroxide saga. *Cutis.* 1995;56:260–261
67. Gollnick HP, Graupe K, Zaumseil RP. Comparison of combined azelaic acid cream plus oral minocycline with oral isotretinoin in severe acne. *Eur J Dermatol.* 2001;11:538–544
68. Espersen F. Resistance to antibiotics used in dermatological practice. *Br J Dermatol.* 1998;139:4–8
69. Eady EA, Jones CE, Tipper JL, Cove JH, Cunliffe WJ, Layton AM. Antibiotic resistant propionibacterium in acne: need for policies to modify antibiotic usage. *BMJ.* 1993;306:555–556
70. Eady EA. Bacterial resistance in acne. *Dermatology.* 1998;196:59–66
71. Meynadier J, Alirezai M. Systemic antibiotics for acne. *Dermatology.* 1998;196:135–139
72. Esterly NB, Furey NL, Flanagan LE. The effect of antimicrobial agents on leukocyte chemotaxis. *J Invest Dermatol.* 1978;70:51–55
73. Esterly NB, Koransky JS, Furey NL, Trevisan M. Neutrophil chemotaxis in patients with acne receiving oral tetracycline therapy. *Arch Dermatol.* 1984;120:1308–1313
74. Webster GF, McGinley KJ, Leyden JJ. Inhibition of lipase production in *Propionibacterium acnes* by sub-minimal-inhibitory concentrations of tetracycline and erythromycin. *Br J Dermatol.* 1981;104:453–457
75. Krowchuk DP. Treating acne: a practical guide. *Med Clin North Am.* 2000;84:811–828
76. Plewig G, Kligman AM. *Acne and Rosacea*. 3rd ed. New York, NY: Springer-Verlag; 2000
77. Goulden V, Glass D, Cunliffe WJ. Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol.* 1996;134:693–695
78. Gough A, Chapman S, Wagstaff K, Emery P, Elias E. Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. *BMJ.* 1996;312:169–172
79. Grosshans E, Belaich S, Meynadier J, Alirezai M, Thomas L. A comparison of the efficacy and safety of lymecycline and minocycline in patients with moderately severe acne vulgaris. *Eur J Dermatol.* 1998;8:161–166
80. Landow K. Dispelling myths about acne. *Postgrad Med.* 1997;102:94–112
81. Thiboutot D, Pariser DM, Egan N, et al. Adapalene gel 0.3% for the treatment of acne vulgaris: a multicenter, randomized, double-blind, controlled, phase III trial. *J Am Acad Dermatol.* 2006;54:242–250
82. Katsambas AD. Why and when the treatment of acne fails. *Dermatology.* 1998;196:158–161