Not Just Skin Deep: New Concepts & Approaches to Acne & "Actinic Keratosis"
CONTINUING MEDICAL EDUCATION

GOAL: To provide dermatologists, residents and dermatology physician assistants with up-to-date information on the treatment and management of patients with acne and actinic keratosis.

TARGET AUDIENCE: This activity is designed for dermatologists, resident and dermatology physician assistants. No pre-requisites required.

LEARNING OBJECTIVES: At the conclusion of this activity, the participant should be able to:

- Recognize the prevalence and pathogenesis of acne to improve treatment outcomes
- Summarize the mechanisms of action and discuss the practical applications of the latest acne treatments
- Evaluate various treatment methods, with specific focus on pharmacologic agents to improve patient quality of life for those affected by acne
- Discuss the pathogenesis, identification process, and differential diagnoses when diagnosing actinic keratosis (AK)
- Describe currently used therapies in the treatment of AK
- Analyze the prognosis for the different stages and the efficacy of treatment options

The Johns Hopkins University School of Medicine takes responsibility for the content, quality and scientific integrity of this CME activity.

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The estimated time to complete this educational activity: 2 hours.

RELEASE DATE: November 15, 2007. EXPIRATION DATE: November 15, 2009. After reading this monograph, participants may receive credit by completing the CE test and evaluation, and receiving a score of 70% or higher.

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Unapproved/unlabeled drug references: No faculty member has indicated that their article will include information on off-label products.
Acne vulgaris and actinic keratosis (AK) are two common skin disorders, which are becoming increasingly prevalent in the United States. As a result, dermatology specialists and patients are becoming more concerned about the sequelae of these conditions and improving patient care.

According to the National Institute of Arthritis and Musculoskeletal and Skin Diseases, nearly 17 million people in the United States have acne. Although acne typically presents during puberty and usually resolves by age 30, it can occur well into adulthood. While self-limiting at times, acne can lead to scarring and psychological anguish. At least four factors are thought to play a role in the pathogenesis of acne, including follicular hyperkeratinization, *Propionibacterium acnes*, inflammation and sebum production. Successful acne management targets these four pathophysiologic factors and reduces the inflammation caused by acne, prevents scarring and reduces the risk of psychosocial comorbidity. Topical retinoids and antibacterial agents address the first three factors, and therefore, are often considered the mainstay of acne treatment. Recent studies demonstrate increasing resistance to early antibiotics used for acne, and this should be taken into account when designing a treatment plan. Clinical investigators have shown that adding a benzoyl peroxide-containing product to the treatment regimen can minimize antimicrobial resistance and increase efficacy. Sebum production is addressed topically by choice of vehicle and skin care. Other options include concomitant oral contraceptives, spironolactone or isotretinoin. Clinical outcomes may be improved by using combination therapy.

Skin cancer is the most widespread of all cancers. More than 1 million cases of nonmelanoma skin cancer are diagnosed annually in the United States, the majority of which are sun-induced. AKs are typically asymptomatic scaly patches and plaques, resulting from chronic ultraviolet exposure and are more prevalent with increasing age. These premalignant lesions serve as a “reliable marker” to identify those individuals at risk for developing squamous cell carcinoma (SCC). The ability to identify and treat AKs before progression to invasive SCC is the most important goal of management. Therapeutic options for AKs include cryosurgery, surgical excision with or without curettage or electrodesiccation, topical pharmaceutical agents and photodynamic therapy (PDT). A combination approach can be used to enhance tolerance, compliance and efficacy. Patient education (ie, the importance of sun protection), monthly self skin examinations and routine skin surveillance by a dermatology professional are vital in the prevention of AKs and subsequent skin cancer.

This supplement to *Skin & Aging* includes the proceedings from a Johns Hopkins CME symposium held on August 3, 2007, in New York, NY. The primary objective was to reinforce and enhance the clinician’s knowledge of the pathogenesis and recognition of acne and AKs, while focusing on effective treatment to achieve optimal patient outcomes.

In the opening article, Susan C. Taylor, M.D., from Columbia University, in New York, NY, presents a concise synopsis of the etiology and psychological impact of acne. She then evaluates current management strategies for acne, with an emphasis on reducing the risk of antibiotic resistance and post-inflammatory hyperpigmentation, particularly in patients with skin of color. Next, Joseph L. Jorizzo, M.D., from Wake Forest University School of Medicine in Winston-Salem, NC, provides an overview of AK, focusing on the prevalence and risk factors, evolution to SCC, histology and prevention. Treatment goals and a variety of management options are subsequently reviewed.

The supplement concludes with four case studies presented by Julie C. Harper, M.D., from the University of Alabama at Birmingham. She applies the novel information presented by her colleagues to clinical practice by designing treatment plans for different patients.

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References

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Acne is by far the most common cutaneous disorder with a high prevalence in children, adolescents and adults. Approximately 80% of patients with acne developed their first skin lesions by age 11. Although acne usually resolves by age 30, in some patients, acne persists far into adulthood. Active physical findings of acne, as well as post-inflammatory hyperpigmentation (PIH) and scarring, can have a profound psychosocial impact. Current therapies target noninflammatory and inflammatory acne lesions, decrease PIH and scarring, and minimize the risk of developing antibiotic resistance.

THE ETIOLOGY OF ACNE

Although the pathogenesis of acne is not completely understood, several factors are thought to play a role in the development of inflammatory/noninflammatory lesions. The etiology of acne involves follicular hyperkeratinization, sebaceous gland activity and the proliferation of Propionibacterium acnes. Of course, the anaerobic bacterium is not only increased in the skin, but it is also responsible for the inflammatory and immune hypersensitivity events. The hyperproliferation of the ductal keratinocytes leads to occlusion or plugging of the follicle, and the onset of the primary precursor lesion of acne, which is the microcomedo (See Figure 1).

Toll-like receptors are a family of proteins that serve as the body’s first line of defense against infection. TLRs, a critical component of the innate immune system, recognize molecular patterns associated with bacterial pathogens and mediate immune responses to microbial ligands. These receptors have been identified on keratinocytes, dendritic cells, monocytes and granulocytes. The structure of the TLRs contains an extracellular and intracellular domain. The extracellular domain contains the pattern recognition receptors that bind conserved molecular structures from the many microbial pathogens, such as lipids. The intracellular domain is homologous to the IL-1 receptor and shares common signaling components with the transcription nuclear factor (NF-κB) pathway.

P. ACNES

P. acnes is a common, normal constituent of the continuous flora, relatively slow growing, aerotolerant anaerobic Gram-positive bacterium, most notably recognized for its role in acne vulgaris. Evidence supports a major role for this anaerobic diphtheroid in the pathogenesis of inflammatory acne. P. acnes can activate chemotactic factors and pro-inflammatory mediators, including lipases, proteases and hyaluronidases, leading to the development of inflammatory acne or inflammation. Activation of the compliment pathway and stimulation of cytokine release by macrophages through toll-like receptors (TLRs) also drives inflammatory disease.
PSYCHOLOGICAL IMPACT OF ACNE

It is important not to underestimate the psychological impact of acne. Gupta and Gupta12 looked at the psychological impact of acne and psoriasis, using the Carroll Rating Scale for Depression to determine the prevalence of depression and suicidal ideation among patients with dermatologic conditions. A score greater than 10 is consistent with clinical depression. They found that in patients with non-cystic facial acne (n=72), a large percentage scored in the range of depression (mean score, 11.2), which was similar to patients with psoriasis (n=138; mean score, 13.4). Findings suggest that even mild-to-moderate facial acne can be associated with significant depression and suicidal ideation. This underscores the importance of recognizing depression as a psychiatric comorbidity and the emotional impact of acne on patients should not be taken lightly.

TREATMENT OF ACNE

There is a confusing array of treatment options. However, by targeting the various factors that trigger acne, the clinician can design a systematic treatment regimen. Topical agents include benzoyl peroxide, retinoids (eg, tretinoin, adapalene and tazarotene) and antibiotics. Systemic acne therapy includes oral antibiotics (eg, erythromycin, tetracycline, doxycycline and minocycline), hormonal agents (eg, oral contraceptives and spironolactone) and isotretinoin. Combination topical agents have been shown to be more effective than using single agents alone.

What Is New?

Research has brought several new developments to the acne forefront, and studies appear favorable. Adapalene is now available in a stronger 0.3% strength, clindamycin has been paired with 0.025% tretinoin in a combination product, and benzoyl peroxide has been shown to minimize antimicrobial resistance in P. acnes, with or without the addition of topical antibiotics.

Adapalene 0.3% gel. Adapalene 0.3% gel was recently FDA-approved. Thiboutot et al13 performed a multi-centered (653 subjects ≥12 years old in 33 centers), double-blind, randomized (2:2:1) trial in which they compared the efficacy of 0.3% adapalene gel with 0.1% adapalene gel versus vehicle for 12 weeks. The primary endpoint was clearing — either total clearing or almost total clearing. The results indicated that almost 25% of patients in the 0.3% adapalene group were rated as clear or almost clear. About 17% of patients in the 0.1% adapalene group were rated as clear or almost clear. This compares to 10% of the vehicle control. This particular study had a diverse group of individuals (approximately 70% white, 10% black, 12% Hispanic and 4% Asian).

When evaluating the adverse events (ie, erythema, scaling, dryness, stinging and burning) of the 0.3% versus the 0.1% adapalene, there were more adverse events in the 0.3% adapalene group (approximately 22%) compared to approximately 12% in the 0.1% adapalene group. Adapalene gel 0.3% was associated with a significantly greater treatment success rate and reduction in total and inflammatory lesion count from baseline than adapalene 0.1% or vehicle gel. Although the study indicates increased efficacy with 0.3% adapalene gel compared to the 0.1% version, adverse events are also increased with the 0.3% adapalene gel. However, the authors confirmed that all of the therapies were well tolerated.

Clindamycin 1%/tretinoin 0.025% versus each agent alone. James Leyden, M.D., et al14 evaluated two randomized, double-blind controlled trials (n=2,219), looking at the efficacy and safety of a combination of clindamycin 1% concentration with tretinoin 0.025% concentration, compared to each ingredient alone, as well as a placebo for 12 weeks. They found that the combination of clindamycin 1%/tretinoin 0.025% in one product out-performed both clindamycin 1% or tretinoin 0.025% alone or vehicle control. Adverse events reported included dryness, desquamation, burning, erythema, pruritis, sunburn and irritation (combination: 19%, clindamycin 1%: 5%, tretinoin 0.025%: 17%, vehicle: 5%).

Clindamycin 1.2%/tretinoin 0.025% versus each agent alone. A combination of three trials (Study 1: n=1,252; Study 2: n=1,288; Study 3: n=2,010) reported by Schlessinger and Plott15 compared clindamycin 1.2% and tretinoin 0.025% combination therapy versus each alone versus vehicle. Inclusion criteria were 20 to 100 noninflammatory lesions, 20 to 50 inflammatory lesions, and two or fewer nodules. Primary endpoints were Evaluator's Global Severity Scale of “clear” or “almost clear” or at least two grades of improvement, and the percent improvement in two of three lesion counts (inflammatory, noninflammatory and total) from baseline to week 12. Similar to the previous study, the percent of patients who achieved the primary efficacy endpoint of clear or almost clear was superior with the combination product at 25% compared to 19% in the clindamycin 1.2% group, 17% in the tretinoin group.
0.025% group and 10% in the vehicle group. Adverse events included itching, burning and stinging (combination: 27%, clindamycin 1.2%; 22%, tretinoin 0.025%; 27%, vehicle: 22%).

In summary, several different trials have demonstrated the combination of clindamycin coupled with tretinoin was effective or more efficacious than both monotherapies in achieving either clear or almost clear status. This combination has shown a significant ability to reduce inflammatory, non-inflammatory and total lesion counts in acne vulgaris.

6% benzoyl peroxide in antibiotic-resistant P. acnes. A major concern in the treatment of acne is antibiotic resistance. Leyden performed a study in which he evaluated resistant P. acnes strains and treated those patients with a 6% benzoyl peroxide wash. There were 30 patients enrolled with P. acnes strains resistant to erythromycin, tetracycline, doxycycline or minocycline. These patients washed daily for 3 weeks. They were supervised and subsequent counts were obtained. Total P. acnes and individual antibiotic-resistant strain counts were obtained at baseline and after weeks 1, 2 and 3.

After week 1 of therapy with 6% benzoyl peroxide wash, a significant reduction of the total resistant P. acnes strains was found. After week 3, there was a greater than 2 logarithm reduction in total P. acnes (ie, in all antibiotic-resistant strains). Results suggest that daily washing with 6% benzoyl peroxide wash reduces antibiotic-sensitive and antibiotic-resistant strains of P. acnes after week 1 of therapy, which is helpful information concerning the use of benzoyl peroxide in treating patients with acne. Combination products containing benzoyl peroxide and the topical antibiotics have been shown to both prevent the development of antibiotic resistance in patients with acne and confer significant clinical improvement to patients who have already developed antibiotic resistance.16

Tazarotene versus tazarotene plus clindamycin 1%/benzoyl peroxide 5%. Tanghetti et al17 evaluated a multi-centered, randomized, double-blinded parallel-group trial with 121 patients with moderate-to-severe acne. They compared the adjunctive use of clindamycin 1%/benzoyl peroxide 5% gel or vehicle gel every morning in combination with tazarotene cream 0.1% every evening in patients with moderate-to-severe inflammatory acne. Patients were treated for 12 weeks. Primary endpoints included comedo and inflammatory lesion counts. Secondary endpoints included adverse events. They concluded the combination of using clindamycin 1% and benzoyl peroxide 5% gel in the morning and tazarotene cream 0.1% at night resulted in significantly greater reduction in comedo count versus tazarotene monotherapy (mean reduction, 70% vs 60%). Among patients with a baseline papule and pustule count greater than 25, a significantly greater reduction in inflammatory lesion count was noted (mean reduction, 63% vs 52%) with the combination. A lower incidence of peeling (10% vs 18% and dryness 8% vs 12%) was a favorable benefit of the coupled agents.

SKIN OF COLOR: ACNE AND HYPERPIGMENTATION

According to several practice surveys, acne vulgaris and particularly PIH comes out in the top 10 diagnoses of practice surveys involving patients with skin of color.18,19 With skin of color patients, early and aggressive management is essential to prevent PIH and scarring. Frequently, these patients present with the chief complaint of dark marks or blemishes. It is the PIH that truly concerns them because those pigmented macules can last for months, whereas an acne lesion typically resolves within 1 week or so (See Figure 3).20 It is important to balance aggressive efficacy with non-irritating topical therapy that does not inflame uninvolved skin.

Treatment of Hyperpigmentation and Acne in Patients of Color

When treating patients with skin of color, therapy should target acne as well as PIH. An additional depigmenting agent may be necessary. Maintenance therapy to prevent the formation of new comedones leading to acne and PIH, coupled with sunscreens, should be emphasized in the treatment of patients with skin of color. In addition, clinicians should advise these patients to avoid the sun and use sun protection.

In a 12-week, multicentered (41 centers), investigator-blind, randomized, prospective, community-based trial (n=353), Kirck et al compared the efficacy and tolerability of the combination of 1% clindamycin/5% benzoyl peroxide gel (C-BPO) coupled with tretinoin microsphere (RAM) 0.04%, RAM 0.1% or adapalene gel 0.1% in a subset of patients of color with moderate-to-severe acne.21 In addition to assessing improvement of the acne, PIH was evaluated in the skin of color population. C-BPO was used in the morning, and a different retinoid was used at night (ie, RAM 0.04%, RAM 1% or adapalene gel 0.1%). Approximately 50% of the patients enrolled were Caucasian and 50% were patients with skin of color.21,22

Hyperpigmentation was assessed using a 6-point scale with 0 being absent and 5 being very severe. The overall population...
started out with slight hyperpigmentation at baseline. After 4, 8 and 12 weeks of therapy with RAM 0.04%, adapalene gel 0.1% or RAM 0.1%, a decrease in the severity of the hyperpigmentation with all three retinoids for the overall population was noted. Looking at the skin of color cohort, including Asians, Hispanics and African-Americans, total hyperpigmentation was rated at slight-to-mild (1.75). Although there was efficacy with the RAM 0.1% and a suggestion with the adapalene gel 0.1%, the mean change from baseline (p=0.0045) of the total skin of color cohort in regard to hyperpigmentation indicated that the RAM 0.04% performed best. The author suggests that the combination of C-BPO and a topical retinoid would be beneficial for acne and PIH, no matter the retinoid.21

The African-American subset of patients started out with mild-to-moderate (2.35) hyperpigmentation at baseline. After 4, 8 and 12 weeks, a subtle trend toward improvement of PIH was noticed with the RAM 0.04% and adapalene gel 0.1%. There was a trend toward more rapid and greater resolution of PIH in the combination C-BPO + adapalene gel 0.1% treated African-American patients. In the Hispanic population, the mean baseline severity was slight-to-mild (1.6), and after treatment, the mean change was quite significant in the RAM 0.04% group with some improvement in the adapalene gel 0.1% group. Finally, the Asian cohort’s baseline hyperpigmentation was slight (1.17), but improvement was indeed noticed as the study progressed, particularly with the RAM 0.04%. There was a trend toward more rapid and greater resolution with the combination C-BPO and the adapalene gel 0.1% and the RAM 0.04% in the Asian cohort.22 However, all three retinoids in combination with C-BPO can help reduce hyperpigmentation, while clearing acne in patients of color.

**Tazarotene 0.1% Cream**

Grimes and Callender23 evaluated tazarotene 0.1% cream for PIH and acne vulgaris in darker skin in a multi-centered (two centers), double-blind, randomized, vehicle-controlled study (n=74). Subjects had mild-to-moderate facial acne and acne-induced PIH with noticeable pigmenary lesions. Tazarotene 0.1% cream versus vehicle was used once daily for up to 18 weeks and was effective in reducing PIH. Compared to vehicle, tazarotene resulted in significantly greater global improvement for PIH and acne, reductions in overall disease severity for PIH and acne, reductions in pigmentary intensity of hyperpigmented lesions and reductions in area of hyperpigmented lesions.

**CONCLUSIONS**

Acne and the sequelae can deeply impact individuals physically and emotionally. Several new acne therapies have been shown to be safe and efficacious, while minimizing the resistance of *P. acnes* and PIH. Concomitant treatment of PIH is crucial for skin of color patients with acne. The mechanism of action is still unknown for hyperpigmentation. An additional depigmenting agent may still be required for optimum results. All topical retinoids have shown efficacy at decreasing epidermal pigmentation while minimizing follicular hyperkeratinization. Furthermore, using retinoids in combination with C-BPO has been shown to reduce antibiotic resistance and hyperpigmentation in patients with acne. Remember that reinforcing education on daily sun protection is essential, even to those patients with skin of color. ■

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**References**


21. Kircik L. Community-based trial results of combination clindamycin 1%-benzoyl peroxide 5% topical gel plus tretinoin microsphere gel 0.04% or 0.1% or adapalene gel 0.1% in the treatment of moderate to severe acne. *Cutis.* 2007;80:10-14.


ACTINIC KERATOSIS: A CLINICAL UPDATE

JOSEPH L. JORIZZO, M.D.

Actinic keratosis (AK) is seen commonly in dermatology practice. Although it is still being debated, many believe that AK actually represents an incipient form of squamous cell skin cancer (SCC). When evaluating a biopsy under a microscope, the histologic features of a hyperplastic AK and SCC are similar. AKs are, at the very least, considered to be precancerous. More than 1 million new cases of skin cancer are diagnosed in the United States each year, and of those, an estimated 200,000 to 300,000 individuals are diagnosed with SCC each year; therefore, it is important to treat AKs to avoid the progression to invasive SCC.

Studies have shown that more than 5 million Americans have at least one AK. Risk factors include fair-skin phenotype, geographic location (ie, closeness to equator), immunosuppression (eg, HIV-positive patients, those receiving organ transplants and patients with cancer) and supplementary sources of ultraviolet radiation (ie, artificial tanning and occupational exposure). The prevalence dramatically increases with age, which is indicative of the strong correlation between the amount of cumulative sun exposure and the occurrence of AK, as well as the fact that immune surveillance lessens with age. Occurrence of AK is higher in men than in women. In a survey conducted in Tennessee, 26.5% of men and 10.2% of white women had one or more AKs. By age 75, 63.6% of the men had AKs. Prevalence also increases with proximity to the equator. In Australia up to 60% of the population older than 40 years has AKs.

AK PROGRESSION TO SCC

One concern in the treatment of AK is preventing progression to invasive SCC, a disease that may account for up to 34% of deaths from skin cancer among persons aged 65 to 84 years. The progression of AKs to SCC occurs in 0.1% to 10% of cases, and 3% of these SCC metastasize. Although AK lesions have markers that show all the features of SCC, they are held in check at the early stage by cellular immunity. Decreasing immune surveillance with increasing age and immunosuppression from chemotherapy, HIV infection or immunosuppressant medications in transplant patients results in increased development of AKs. Immunosuppression is an important factor in the concept of AKs, in situ SCC and invasive SCC as a continuum, and should be kept in mind when treating patients with AKs.

Chronic progression of AKs to SCC correlates with the evolution of histologic features. Characteristics include epidermal hyperplasia with a partial-thickness proliferation of keratinocytes exhibiting cytoplastic atypia, loss of polarity, nuclear pleomorphism and disordered maturation. As it progresses to invasive SCC, proliferations may be long and slender or bulbous extensions into the papillary dermis. In Figure 1, underlying solar elastosis of the dermis coupled with extension of atypical cells along adnexal structures suggests SCC; however, the atypia is not full thickness and considered to be premalignant. Given enough time, 0.1% to 10% of AKs will progress to SCC.

PREVENTION OF AK

Prevention is fundamental in the management of AKs and photoaged skin. It is important to inform patients of the risks of AK and advise them to avoid excessive exposure to sunlight during peak sunlight hours (10 a.m. to 4 p.m.); avoid prolonged periods around reflective surfaces, such as water; wear protective clothing and a wide-brimmed hat; and apply a broad-spectrum (UVA/UVB) sunscreen (sun protection factor 15 or higher) liberally. Reliable data now show that ultraviolet light induces a suppressor T-cell subset, which suppresses immune surveillance and allows for progression of AKs to SCC. Using daily sunscreens that block UVA and UVB light can greatly reduce the incidence of AKs and subsequent skin cancer.

TREATMENT GOALS AND OPTIONS

When treating photoaged skin, the primary goal is eradication of AKs to prevent future morbidity. However, it is becoming more common for patients to expect dermatologists to provide comprehensive wellness care for diseases of the skin, so the secondary goal is to improve the cosmetic appearance, self-esteem and, ultimately, quality of life. This can be done with elective treatments, such as chemical peels and laser resurfacing, which may reduce signs of photodamage, including fine lines/wrinkles, textural alterations, diffuse dyschromias, yellowing and mottling of the skin.
A variety of treatment options are available for the treatment of AKs — cryosurgery, curettage/shave removal, chemical peels, photodynamic therapy (PDT) and topical therapies. Combination therapy often is most effective. When selecting a treatment, there are several factors to consider, including a patient’s overall risk of SCC; the types, number and locations of lesions; patient preference; cosmetic prognosis; and cost.

**Cryosurgery**

Cryosurgery is one of the most convenient methods to treat AKs, and most dermatology offices are equipped with liquid nitrogen. It is often more efficient to examine patients with such an agent at hand, particularly for those with a history of hypertrophic AK. AK lesions are more sensitive to cryotherapy compared to normal cells, and it can treat multiple lesions quickly.

Studies have shown that cryotherapy has up to a 99% success rate 1-year post-surgery.20 Adverse effects include local erythema, blisters, crusts, weeping, pain and secondary infection. Hypopigmentation is a common and undesirable sequelae of cryotherapy.11 It can be reduced by using the least possible amount of cryosurgery and then properly taking care of the wound to prevent secondary infection or other effects that could lead to hypopigmentation. Provide patients with instructions for care of wounds and reinforce the importance of compliance.

**Curettage/Shave Removal**

Extensive photodamage often parallels the number of suspicious lesions that patients present with, thus it can be difficult to distinguish between AK and SCC clinically. Removal of AK lesions with curettage/shave removal permits histologic examination and a 95% to 99% success rate has been reported. Adverse effects include pain, scarring, and hypo- or hyperpigmentation.11

**PDT**

Photodynamic therapy is a novel modality used to treat AK that has shown promise in respect to efficacy and tolerance. Aminolevulinic acid (ALA) plus light involves the topical application of 20% ALA. It preferentially localizes in the abnormal AK/SCC cells and upon exposure to blue light, ALA is converted to protoporphyrin IX, which produces oxygen intermediates that destroy the abnormal AK/SCC cells. Efficacy of ALA is well established.21

**Topical Therapy**

Topical therapy is available in a variety of creams and solutions. The tolerability of reactions, duration, size availability, and cost differs for each product as shown in Table 1.22,23

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<tr>
<th>Product</th>
<th>Duration</th>
<th>Size Availability</th>
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<tbody>
<tr>
<td>Imiquimod 5%</td>
<td>4 weeks</td>
<td>60g</td>
</tr>
<tr>
<td>3% diclofenac gel</td>
<td>90 days</td>
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**Imiquimod 5%**. This novel immune response modifier can be used to treat multiple AK lesions97 and does not require surgery. Although the exact mechanism of action remains unclear, it appears that this treatment uses the immune system to reject these AK lesions from below. A phase III, randomized, multi-centered (18 centers), double-blind, parallel group, vehicle-controlled study (n=286) evaluated the efficacy of imiquimod 5% cream compared with vehicle in the treatment of AK of the face and scalp. The 3% diclofenac gel was used for 90 days and the 5-FU cream for 28 days. Both demonstrated significant efficacy; however less inflammation was demonstrated with 3% diclofenac gel, despite the longer treatment period of 60 to 90 days. This generated significant patient satisfaction. Also, photosensitivity or phototoxicity is not induced with 3% diclofenac gel alone or in combination with sunscreens.20

**3% diclofenac gel**. 3% diclofenac gel is a well-known, nonsteroidal anti-inflammatory drug used for arthritis that can be used to treat AK, although the mechanism of action is unknown. This novel formulation (3% diclofenac in 2.5% hyaluronan gel) can be used to treat multiple AKs and does not require surgery.24 A comparison study (n=30) was conducted by Smith et al,25 which evaluated the efficacy and tolerability of 3% diclofenac sodium gel and 5-fluorouracil (5-FU) cream in the treatment of AK of the face and scalp. The 3% diclofenac gel was used for 90 days and the 5-FU cream for 28 days. Both demonstrated significant efficacy; however less inflammation was demonstrated with 3% diclofenac gel, despite the longer treatment period of 60 to 90 days. This generated significant patient satisfaction. Also, photosensitivity or phototoxicity is not induced with 3% diclofenac gel alone or in combination with sunscreens.20

**Topical 0.5%-FU**. Topical 0.5%-FU inhibits DNA synthesis, leading to impaired AK growth when compared to growth of normal cells. It is available in once-daily formulation and can be used to treat multiple and subclinical lesions26; surgery is not required. Typical adverse effects, such as burning, itching, redness, flaking and peeling, can be managed with the application of topical hydrocortisone (0.5% to 1.0%). Weiss et al conducted a randomized, double-blind, multicentered, parallel-group study (n=177) to evaluate safety and efficacy of 0.5%-FU compared with vehicle once daily for 1, 2 or 4 weeks.
Efficacy was assessed by lesion counts and clearance and safety was gauged by monitoring for adverse events. Of those treated with 0.5%-FU at 4 weeks, 88.7% had a reduction in lesions and 47.5% achieved total clearance, which was significantly higher compared to vehicle (34.4% and 3.4%, respectively). Mild-to-moderate facial irritation was the primary adverse event, which lasted 15 to 17 days post-treatment.

Interval (pulse) therapy with 5-FU. Although there is a known risk of burning, itching and inflammation with all formulations of topical FU, there has been well documented evidence that FU acts as chemotherapy and suppresses inflammation when used alone or in combination. An excessive inflammation response is not necessary when using FU to achieve reduction of AK, and all AK treatments typically involve a localized inflammatory response, which can be socially disruptive. Interval (pulse) therapy with 5-FU can potentially overcome such adverse, unwelcome reactions, without reducing efficacy. It often involves varying the frequency of application, which allows for delivering a lower than recommended dose. In a study by Pearlman, 10 patients completed an interval (pulse) therapy study using topical 5-FU for multiple facial AKs and applying it 1 to 2 days per week for an average of 6 to 7 weeks. This method cleared 98% of the lesions. Irritation was limited to erythema without disruption to their social or business lives due to altered appearance. At 9 months, six available patients remained 86% clear of lesions. This study suggests efficacy can be obtained without excessive irritation.

Chemical Peels
Chemical peels are useful for cosmetic facial rejuvenation and eliminating photoaging skin and AKs (See Figure 2). Peels may be performed at superficial, medium or deep levels, depending on the extent of damage. Side effects include stinging, irritation and inflammation. Combination therapy with 5-FU also can be considered.

Combination Therapy
There is no ideal monotherapy for the treatment of AK, thus combination therapy is often used because it has the potential to enhance treatment efficacy. Diverse combination therapies are available, including cryotherapy plus a choice of topical therapy; shave removal followed by topical therapy; and topical retinoids followed by 5-FU. There are ongoing studies of the efficacy of different combination therapies. One such study was a recent prospective, multi-centered, randomized, double-blind, vehicle-controlled clinical trial (n=144, ≥5 facial AK lesions). Investigators examined the 6-month outcome of a 1-week course of 0.5%-FU followed by cryosurgery. Topical 0.5%-FU was used once daily for 7 days. At 4 weeks follow-up, the remaining lesions were treated with cryosurgery. The primary endpoints were reduction in AKs from baseline to 4 weeks and 6 months. At 4 weeks, the mean AK lesion count reduced by 62.4% in the 0.5%-FU group versus 28.8% in the vehicle group, and complete clearance was achieved in 16.7% of patients in the 0.5%-FU group versus 0% in the vehicle group. At 6 months, the mean lesion count was reduced by 62.4% in the 0.5%-FU plus cryosurgery group and significantly more patients had complete clearance (30%) in the 0.5%-FU plus cryosurgery group than vehicle group (7.7%). Although the mean lesion count was reduced with the addition of cryosurgery at week 4, there was still a high occurrence of AKs at 6-month follow-up, showing the need for continued surveillance.

Cosmetic Considerations
Individuals desire products that do not feel heavy or greasy, thus new formulations are being developed to address these concerns. This can be seen with the latest “microsphere” vehicle formulation of 0.5%-FU, which has a more favorable irritation profile than the precursors and is preferred by patients. In addition, treatments, such as chemical peels, which enhance appearance while treating AKs, are being used more often. Other options include laser resurfacing, non-invasive lasers, radiofrequency devices, hyaluronic acid gels, poly-L-lactic acid injections, permanent...
fat injections and botulinum toxin injections. By including cosmetic considerations in AK treatment, specialists in dermatology can provide comprehensive wellness for the skin that improves the patient’s self-esteem and quality of life.

CONCLUSIONS

When managing the treatment of AK, it is important to remember that it can never be considered "cured." Long-term surveillance is necessary, especially because the incidence of AK increases with age and is often seen with other signs of aging. Although the primary goal in AK treatment is always to prevent future morbidity from cancer, aesthetic and wellness considerations are also important to patients. Overall patient outcomes can be significantly improved by providing a treatment plan that provides individualized patient care and comprehensive wellness for the skin.

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References


TABLE: Topical Therapy Options for AK

<table>
<thead>
<tr>
<th>Concentration (Formula)</th>
<th>Application</th>
<th>Available Sizes</th>
<th>AWP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% imiquimod cream</td>
<td>Twice weekly for 16 wk</td>
<td>12 packets</td>
<td>$268.38</td>
</tr>
<tr>
<td>Microsphere-encapsulated 0.5% FU cream</td>
<td>Once daily for 1–4 wk</td>
<td>30-g tube</td>
<td>$143.73</td>
</tr>
<tr>
<td>5% FU cream</td>
<td>Twice daily for 2–4 wk</td>
<td>40-g tube</td>
<td>$249.05</td>
</tr>
<tr>
<td>5% FU solution</td>
<td>Twice daily for 2–4 wk</td>
<td>10-mL bottle</td>
<td>$249.05</td>
</tr>
<tr>
<td>1% FU cream</td>
<td>Twice daily for 2–6 wk</td>
<td>30-g tube</td>
<td>$139.15</td>
</tr>
<tr>
<td>3% diclofenac gel</td>
<td>Twice daily for 30–90 d</td>
<td>50-g tube 100-g tube</td>
<td>$198.45 $301.51</td>
</tr>
</tbody>
</table>

*AWP reflects brand name price.

AK = actinic keratosis; AWP = average wholesale price; FU = fluorouracil.

Data from Jorizzo et al and Amerisource database.23

A ctinic keratoses (AKs) and acne are common skin disorders in dermatology. The previous articles provided an overview of the pathogenesis and treatment of acne and AKs. The following four case studies provide examples of how to put this information into practice.

CASE STUDY 1: ACTINIC KERATOSIS

Presentation
A 78-year-old man with a history of squamous cell carcinoma (SCC) and numerous AKs returns for his routine follow-up examination (See Figure 1). He wears a hat and long sleeves when outdoors, but refuses to apply sunscreen. He is not interested in home therapy and prefers to have lesions “burned off” while in the office.

Treatment Options
There are a variety of options for treating patients with AKs. In this case, choices include cryotherapy alone, photodynamic therapy (PDT), or a combination of 0.5% 5-fluorouracil (FU) for 1 week followed by cryotherapy. Each treatment is discussed briefly below, and additional information can be found in the previous article by Joseph L. Jorizzo, M.D.

Cryotherapy. Liquid nitrogen or cryotherapy is the most commonly used treatment for AK. It is a simple and convenient method, which can be done quickly during an office visit. However, there is a significant risk of hypopigmentation, which can be minimized by using a single freeze-saw cycle and reducing the duration of cryotherapy.

PDT. This innovative treatment modality for AK has received FDA approval for lesional therapy, however, “field” therapy remains off-label. Topical 5-aminolevulinic acid (ALA) is converted to protoporphyrin IX, which is a potent photosensitizer. When it is exposed to light, protoporphyrin IX generates oxygen-free radicals, which results in destruction of AKs. There are several potential light sources available, including blue light, intense pulsed light and laser. The efficacy of PDT is comparable to that of 5-FU, and the cosmetic results are good. Side effects include photosensitivity, stinging and burning. Also, the incubation period for 5-ALA and the cost can be inconvenient for patients.

0.5%-FU for 1 week followed by cryotherapy. Often, combination therapy is found to be an effective method for treatment of AKs. With this method, the patient is treated with 0.5%-FU for 1 week. Then, at the 4-week follow-up visit, any residual lesions are treated with cryotherapy. Evaluations were determined at 4 weeks and 6 months. This method was studied in a prospective, multicentered, randomized, double-blind, vehicle-controlled clinical trial, discussed in further detail in Dr. Jorizzo’s article. The study showed those treated with 0.5%-FU had better improvement in lesion counts compared to placebo. This brief 1-week treatment course may be an acceptable alternative for patients who are not interested in a traditional 2- to 4-week course of 5-FU.

Treatment Plan
With this patient, the idea of a 1-week treatment with the topical 0.5%-FU followed by cryotherapy was a practical approach. The use of 0.5%-FU as a “blanket” or “field” treatment would decrease the number of AKs that need to be “frozen off” with cryotherapy. This is a good option for patients who come in every 2 to 3 months with more than 15 lesions.
CASE STUDY 2: ACNE

*Presentation*

You are asked to evaluate a 17-year-old boy with moderate acne who tells you he uses “whatever soap is in the shower.” He has been taking 100-mg minocycline twice a day, which was prescribed by his pediatrician, for 6 weeks with minimal improvement. Examination reveals a healthy adolescent with oily skin, comedones and inflammatory papules and pustules on the forehead, cheeks, chin, back and shoulders (See Figure 2).  

*Treatment Plan*

A treatment regimen should be designed based on the severity of the disease and the patient’s ability to comply with treatment. It is important to target the four factors that trigger acne (see Susan C. Taylor, M.D.’s article): (1) follicular epidermal hyperproliferation; (2) *Propionibacterium acne*s; (3) inflammation; and (4) excess sebum.  

For this patient, a topical retinoid was added to his current regimen to reverse follicular hyperkeratinization, prevent future comedones and provide an anti-inflammatory effect. He was continued on minocycline for the anti-inflammatory effect and to suppress *P. acne*s. A benzoyl peroxide-containing product was added to minimize the emergence of antibiotic-resistant strains of *P. acne* and suppress comedone formation.  

Excess sebum was addressed by vehicle selection (ie, gel) and by discussing appropriate skin care, such as the use of a benzoyl peroxide cleanser or salicylic acid wash.  

At the initial visit, it is important to counsel the patient on the proper use of all medications and discuss potential adverse effects. Setting reasonable expectations of when improvement will be achieved (eg, the patient will see 40% to 50% improvement in 6 to 8 weeks) and discussion of skincare methods to minimize potential irritation is a vital part of patient education. A 6-week follow-up appointment should be scheduled to evaluate the patient’s progress.

*Follow-up*

At a 6-week follow-up visit, the patient demonstrates 40% to 50% improvement. He is tolerating oral and topical medications well, and the current regimen is continued. The patient schedules a follow-up visit. Eight weeks later, an approximate 80% improvement has been obtained. The current regimen is continued and he schedules a follow-up visit in 2 months. At this visit, continued improvement is noted and has been sustained, thus it is necessary to plan maintenance therapy for this patient.

*Maintenance Therapy*

There are several options for maintenance therapy in this patient, including continuing the topical retinoid as monotherapy, continuing the benzoyl peroxide-containing product as monotherapy, continuing with combination topical retinoid and benzoyl peroxide-containing product therapy or tapering to a lower dose of minocycline and continuing with the topical retinoid. In this case, the patient continued with a combination topical retinoid and benzoyl peroxide-containing product therapy, and he continued taking 100-mg minocycline twice a day. Limiting the duration of systemic antibiotics,

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**TABLE 1: Tips to Lessen Antibiotic Resistance During Acne Treatment**

<table>
<thead>
<tr>
<th>Tip</th>
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<tbody>
<tr>
<td>Limit the duration of systemic antibiotic.</td>
</tr>
<tr>
<td>Avoid rotation of antibiotics.</td>
</tr>
<tr>
<td>Avoid concurrent use of oral and topical antibiotics, especially when they are chemically dissimilar.</td>
</tr>
<tr>
<td>- If unavoidable, include a benzoyl peroxide-containing product, either with it or as a wash, to minimize the risk of resistant strains.</td>
</tr>
<tr>
<td>Avoid monotherapy with antibiotics.</td>
</tr>
<tr>
<td>Prescribe medications that do not promote resistance (eg, topical retinoids).</td>
</tr>
<tr>
<td>Add a benzoyl peroxide-containing product to prevent and reduce resistant strains of <em>Propionibacterium acne</em>s.</td>
</tr>
</tbody>
</table>
while adding a benzoyl peroxide-containing product, can prevent and reduce resistant strains of *P. acnes*. Topical retinoids can be continued because they do not promote antibiotic resistance and have the ability to prevent future comedones, follicular hyperproliferation and inflammation.

**Antibiotic Resistance**

It is important to consider the potential for antibiotic resistance when establishing a maintenance therapy routine for patients with acne. Dermatologists are increasingly aware of this problem. Resistance occurs when the bacteria genes for resistance are exposed to chronic antibiotic therapy. This exposure eradicates the susceptible bacteria (target pathogen) and the resistant bacteria (nonpathogenic bacteria) proliferate, thus the number of bacteria can increase. The nonpathogenic bacteria that are resistant to the antibiotic now act as a reservoir of resistant genes that can be transferred to other potentially pathogenic bacteria.

**Combating resistance.** Dermatology specialists can help limit antibiotic resistance of *P. acnes* simply by re-evaluating their individual prescribing practices used for acne and following the suggestions provided in Table 1. If a non-antibiotic topical preparation will suffice, do not prescribe antibiotics. Try to use medications that do not promote resistance (eg, topical retinoids). When an antibiotic is necessary, the duration of use should be brief. If further treatment is required, reuse the same antibiotic whenever possible to avoid resistance to both products. Adding a benzoyl peroxide-containing product to the regimen, as done with this patient, will help prevent and reduce resistant strains of *P. acnes*. Benzoyl peroxide is a broad-spectrum antibacterial agent, which contains oxidized intermediates that interact with and kill microbes. To date, no resistance to benzoyl peroxide has been reported. When used in combination with an antibiotic, benzoyl peroxide prevents the selection of the antibiotic-resistant organisms. Finally, try to avoid concomitant use of chemically dissimilar systemic and topical antibiotics. If a topical antibiotic is necessary, be sure to include a benzoyl peroxide-containing product to minimize resistance.

**CASE STUDY 3: ACNE**

**Presentation**

You are asked to examine a 23-year-old woman who presents with acne. She has already tried “everything” and...
is now using a topical retinoid once daily and has been tak-
ing doxycycline 100 mg twice daily for 8 weeks. She is still
breaking out, particularly on the lower face, jawline and
neck. Physical examination reveals oily skin, a few comed-
dones on her cheeks and nose, two inflamed nodules on
her jawline and several inflammatory papules and erythe-
ma on her chin, neck and cheeks (See Figure 3).

**Treatment Plan**

As with the previous patient, the treatment plan should tar-
get factors that promote the development of acne. Follicular
epidermal hyperproliferation and inflammation are addressed
with the continued used of the topical retinoid. She contin-
ued to take doxycycline 100 mg twice daily to provide an
adjunctive anti-inflammatory effect. Also, by avoiding rotation
of the antibiotic, the risk of *P. acnes* resistance was mini-
mized. A benzoyl peroxide-containing product was added to
her regimen to further reduce the threat of antibiotic-resistant
strains, as well as an oral contraceptive to target the seba-
ceous gland activity and sebum production.

**Oral contraceptives for acne control.** Oral contracep-
tives have been shown to be effective in targeting seba-
ceous gland activity and excess sebum production. How-
ever, improvement in acne is not expected until the oral contraceptive has been taken for 3 months or longer.

Combination oral contraceptive pills decrease androgen production in the ovaries and the amount of circulating androgen by increasing sex hormone-binding globulin. Excess androgen results in the production of excess sebum. It is important to remember that oral contracep-
tives need to be used as supplemental therapy, because they do not target all four causes of acne.

Oral contraceptives are used most safely in women younger than 35 years who do not smoke, do not have migraine headaches and who are normotensive. Although oral contraceptives decrease androgen pro-
duction, the patient’s androgen levels do not need to be abnormal for oral contraceptives to be effective. Any female patient with acne who is not responding appro-
priately to traditional combination therapy and does not have contraindications to oral contraceptives is a candi-
date. Oral contraceptives also can be considered in female patients planning to take isotretinoin or in those who are unable or unwilling to take systemic antibiotics. They may be used early in the treatment of acne, partic-
ularly when they are also being used for another indication (eg, desire to prevent pregnancy or premenstrual dysorphic disorder). In addition, women with signs of hyperandrogenism (eg, hirsutism or abnormal/irregular menstrual periods) may benefit from the antiandrogen effects of oral contraceptives.

An appropriate laboratory evaluation should be per-
formed before beginning treatment with an oral contracep-
tive only if there are signs of hyperandrogenism. Make sure
the patient has not taken oral contraceptive pills for at least
6 weeks before laboratory analysis for an endocrine disor-
der. Also avoid testing near ovulation; advise laboratory
tests be taken during menses or 1 week before. Tests
should include serum dehydroepiandrosterone sulfate
(DHEAS), free and total testosterone, luteinizing hor-
monene/follicle-stimulating hormone ratio (>3 indicates polycystic ovarian disease) and 17-hydroxyprogesterone (helps determine androgen etiology [adrenal or ovarian]).

A list of contraindications is provided in Table 2, and three methods for beginning oral contraceptive treatment in acne are listed in Table 3.

**Spironolactone for acne control.** Another option for reduc-
sebum production is oral spironolactone. Spironolactone is an aldosterone antagonist that binds the androgen receptor. It inhibits androgen biosynthesis in the gonads and adrenal gland and suppresses 5 α-reductase activity in the sebaceous gland. Adverse effects, which are typically dose related, include polyuria, menstrual disturbances, gynecomastia, dizziness, headache and weight gain. Guidelines for the use of spirono-
lactone are provided in Table 4.

A survey study with comparison chart review evaluated the long-term safety and tolerance of spironolactone in women with acne. The women, followed for up to 8 years, had favorable results. Ninety-one surveys were analyzed, comprising 506 person-years of follow-up and 200 person-
years of spironolactone exposure. The mean length of treat-
ment was 28.5 months. During the 8-year follow-up period,
there were no cases of serious illness as a result of the use of spironolactone. The most common side effects experi-
enced were diuresis and menstrual irregularities. Of those,
15% resulted in discontinuation of the drug. Long-term use
of this agent appeared to be safe.
In a separate open-labeled prospective study, the side effects of spironolactone and how it affected serum blood levels were examined.\(^6\) In the study, 35 women were given spironolactone 100 mg/day for 16 days each month for 3 months. DHEAS and total testosterone levels were measured before and after treatment. Clinically significant improvement was noted in 85.7% of patients who had corresponding decreased DHEAS levels after treatment. There was no change in the total testosterone levels. The most common side effect reported was menstrual irregularities. The authors reported safety and efficacy, while suggesting spironolactone be offered as an alternative choice for women with acne vulgaris.

**CASE STUDY 4: ACTINIC KERATOSIS**

**Presentation**

A 62-year-old woman with a fair complexion is evaluated for numerous AKs on her lower extremities (See Figure 4).\(^21\) Two skin biopsies were performed and both showed AKs. She has never had skin cancer and denies a history of arsenic exposure.\(^21\) She does have a long history of sun exposure.

**Treatment Plan**

Skin cancer is the most common form of human cancer.\(^22\) AKs and SCC have common features (see previous article by Dr. Jorizzo),\(^22\) and if left untreated, AKs can progress to SCC.\(^24\)

You decide the optimal treatment for this patient is a topical retinoid in combination with topical 5-FU. A topical retinoid accelerates the penetration of this antimitotic agent. The synergistic effect of these two topical agents has been demonstrated in a randomized, double-blind trial (n=19).\(^25\) In this study, 5-FU cream was applied twice daily, followed by 0.05% tretinoin cream nightly to one arm, and a control cream was applied to the opposite arm until discomfort curtailed further applications. It was concluded that the daily application of 0.05% tretinoin cream appeared to enhance the efficacy of topical 5-FU in destruction of AK of the arms.

**CONCLUSIONS**

There are many factors to consider when deciding how to treat patients with AK or acne. When managing patients with AKs, it is important to identify, treat and prevent the lesions, because 0.1% to 10% progress to SCC. Individualized education and surveillance is essential to prevent morbidity. For patients with acne, it is important to create a treatment plan that targets the factors that cause acne. Using combination therapy is an effective way to accomplish this. Adding a benzoyl peroxide-containing product to topical antibiotics reduces the risk of selecting resistant *P. acnes*. The addition of oral contraceptive pills for women can result in further improvement. Negotiating with patients about vehicles, general skin care and frequency of application of topical agents and administration of oral agents can improve patient comfort and enhance compliance.

**References**

**NOT JUST SKIN DEEP: NEW CONCEPTS & APPROACHES TO ACNE & “ACTINIC KERATOSIS”**

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**INSTRUCTIONS**

After reading “Not Just Skin Deep: New Concepts & Approaches to Acne & “Actinic Keratosis,” select the 1 best answer to each of the following questions. At least 7 of 10 answers must be correct to receive CME credit. Estimated time for reading this issue and taking the test is 2 hours.

1) **WHICH OF THE FOLLOWING IS FALSE ABOUT ACTINIC KERATOSES (AKs)?**
   - a. AKs and squamous cell carcinoma (SCC) have common features.
   - b. Untreated AKs progress to SCC 0.1% to 10% of the time.
   - c. AKs should always be excised.
   - d. AKs are treatable and can be managed.
   - c. Spironolactone is safe during pregnancy.
   - d. Spironolactone inhibits androgen biosynthesis in the gonads and adrenal gland.

7) **WHICH OF THE FOLLOWING STATEMENTS ABOUT PHOTODYNAMIC THERAPY (PDT) IS FALSE?**
   - a. PDT gives an excellent cosmetic outcome.
   - b. PDT is effective and convenient.
   - c. PDT is not as effective as 5-fluorouracil (5-FU).
   - d. Photosensitivity is a common side effect of PDT

8) **WHICH OF THE FOLLOWING IS THE MOST COMMONLY USED THERAPY FOR AKs?**
   - a. Cryotherapy
   - b. PDT
   - c. 5-FU followed by cryotherapy for residual lesions
   - d. Imiquimod

9) **WHICH OF THE FOLLOWING STATEMENTS ABOUT COMBINATION ORAL CONTRACEPTIVE PILLS IS TRUE?**
   - a. Combination oral contraceptive pills increase androgen production in the ovaries and decreases sex hormone-binding globulin.
   - b. Combination oral contraceptive pills decrease androgen production in the ovaries and decreases the amount of circulating androgen by increasing sex hormone-binding globulin.
   - c. Combination oral contraceptive pills are used most safely in women with a history of migraines.
   - d. Combination oral contraceptive pills are used most safely in women older than 35 years.

**10) WHAT MEASURES HAVE PROVEN TO BE EFFECTIVE IN REDUCING THE DEVELOPMENT OF ANTIMICROBIAL RESISTANCE DURING ACNE THERAPY?**
   - a. Use medications, such as topical retinoids, that do not promote resistance.
   - b. Limit the duration of topical and systemic antibiotics.
   - c. Add a benzoyl peroxide containing product to prevent and reduce resistant strains of *P. acnes*.
   - d. All of the above
CONTINUING MEDICAL EDUCATION EVALUATION

**PROGRAM EVALUATION**

**NOT JUST SKIN DEEP: NEW CONCEPTS & APPROACHES TO ACNE & “ACTINIC KERATOSIS”**

Your evaluation of the CME content is an integral part of this activity. To complete your participation and receive your CME credits, please complete the questionnaire below.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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<td>❑❑</td>
<td>❑❑</td>
<td>❑❑</td>
</tr>
</tbody>
</table>

1. **THIS COURSE MET THE OVERALL OBJECTIVES BELOW:**
   - Recognize the prevalence and pathogenesis of acne to improve treatment outcomes
   - Summarize the mechanisms of action and discuss the practical applications of the latest acne treatments.
   - Evaluate various treatment methods, with specific focus on pharmacologic agents to improve patient quality of life for those affected by acne
   - Discuss the pathogenesis, identification process, and differential diagnoses when diagnosing actinic keratosis (AK)
   - Describe currently used therapies in the treatment of AK
   - Analyze the prognosis for the different stages and the efficacy of treatment options

2. **ARE YOU A PHYSICIAN?**  ❑❑ YES  ❑❑ NO

3. **WILL YOU CHANGE YOUR PRACTICE IN ANY WAY AS A RESULT OF PARTICIPATING IN THIS COURSE?**  ❑❑ YES  ❑❑ NO If yes, please specify:

4. **DO YOU FEEL THE ACTIVITY WAS OBJECTIVE, BALANCED, AND FREE OF COMMERCIAL BIAS?**  ❑❑ YES  ❑❑ NO If no, please specify:

5. **IF PRESENT, WAS OFF-LABEL DRUG AND/OR DEVICE DISCUSSION PROPERLY DISCLOSED?**  ❑❑ YES  ❑❑ NO If no, please specify:

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   a) Quality of the educational content:  ❑❑ Excellent  ❑❑ Good  ❑❑ Fair  ❑❑ Poor
   b) Quality of design and organization:  ❑❑ Excellent  ❑❑ Good  ❑❑ Fair  ❑❑ Poor
   c) Quality of printed/online material:  ❑❑ Excellent  ❑❑ Good  ❑❑ Fair  ❑❑ Poor

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   - Print (Journal/Monograph)  ❑❑ Live Conference  ❑❑ CD-ROM  ❑❑ Audio  ❑❑ Videotape  ❑❑ Online Lessons

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