

CME ARTICLE

Acne Vulgaris: Pathogenesis and Therapeutic Approach

Daniel G. Federman, MD; and Robert S. Kirsner, MD

AUDIENCE

This activity is designed for primary care providers, internists, and general audiences.

GOAL

To provide the reader with a basic understanding of the pathogenesis of acne vulgaris and the rationale behind several treatment options. Clinicians should be aware of treatment strategies for various subtypes of acne vulgaris.

OBJECTIVES

1. To describe the emotional and financial impact of acne.
2. To describe the differential diagnosis of acne vulgaris.
3. To discuss acne's pathogenesis.
4. To provide information on topical therapy for the treatment of acne vulgaris.
5. To discuss oral therapy for the treatment of acne vulgaris.

CONTINUING MEDICAL EDUCATION ACCREDITATION

Johns Hopkins University School of Medicine designates this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association.

Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

From the Department of Medicine, Yale University School of Medicine, New Haven, CT and VA Connecticut Health Care System, West Haven, CT (DGF); and the Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, FL (RSK).

Address correspondence to: Daniel G. Federman, MD, VA Connecticut Health Care System, 950 Campbell Ave (111-GIM), West Haven, CT 06516.

Acne vulgaris, or common acne, is an extremely prevalent disorder that is frequently encountered in the practice of most medical disciplines. Acne is the most common dermatologic disorder and affects 80% of people between the ages of 11 and 30 years.¹ Although acne is usually thought of as a condition of adolescence, 8% of the 25- to 34-year and 3% of the 35- to 44-year age groups are affected.²

Acne remains a major component of a dermatologist's practice, involving approximately 20% of all visits,¹ but is often encountered in the practice of nondermatologists as well. The diagnosis is often readily apparent, and of the 20 most common dermatoses, acne is the one that primary care physicians have the least difficulty correctly diagnosing.³ In fact, patients themselves often come to the physician seeking treatment for their acne.

The economic impact of acne is considerable. The annual cost of nonprescription drugs for acne is nearly \$100 million²; and according to data from the National Ambulatory Medical Care Survey, visits to primary care providers for acne-related disorders have more than doubled from 400,000 per year in 1980-1981 to 900,000 per year in 1989-1991.⁴

Though not life threatening, acne can have severe psychosocial consequences leading to poor self-esteem, social isolation, and depression.⁵ Patients with acne are less successful at gaining employment.⁶ Although in many patients acne may be limited to a few papules or comedones, severe disease may eventuate in scarring and disfigurement.

... PATHOGENESIS ...

The pathogenesis of acne is thought to be due to a complex interaction between abnormal follicular differentiation, androgens, sebum, and the anaerobic

microorganism *Propionibacterium acnes* (*P acnes*) in the sebaceous follicles of the face, chest, and back.

Acne frequently begins in the prepubertal period, when adrenal androgens released by the maturing adrenal gland lead to increased production of sebum, the lipid-rich secretion of the sebaceous glands. As the gonads mature, androgen production increases further, leading to additional sebum production. Acne patients have higher rates of sebum production than patients without acne, and the severity of acne is generally proportional to the amount of sebum production.⁷ Although most patients exhibit hyper-responsiveness to endogenous androgens rather than frank androgen excess, patients with androgen excess frequently develop acne.⁸

Abnormalities in the follicular epithelial differentiation also are thought to play a pivotal role. Abnormal epithelial desquamation in the upper canal of the follicle leads to a thickened stratum corneum and follicular plugging. This occluded follicle, the microcomedo, is the precursor of both inflammatory and noninflammatory acne. Comedones may be closed (whiteheads) or open (blackheads) (Figure 1). The whitehead contains inspissated keratin and lipid debris, whereas the black color of open comedones is due to the oxidation of tyrosine to melanin by tyrosinase through the open pore.

The lipid-rich occluded follicle is an ideal substrate for *P acnes*, an anaerobic diphtheroid that is part of the normal flora of the skin, but that is usually absent from the skin before puberty.⁹ *P acnes* is present in higher quantities in acne patients than those without acne.¹⁰

Flourishing *P acnes* microorganisms elaborate a lipase that hydrolyzes sebum triglycerides into free fatty acids and glycerol, which have proinflammatory and comedogenic properties. *P acnes* leads to further inflammation through its release of chemotactic factors, attracting neutrophils, lymphocytes, and macrophages, which release lysosomal enzymes that cause damage or rupture to the follicular wall.¹¹ *P acnes* proliferation also leads to complement activation and release of other proteases and other hydrolytic enzymes.¹² Dermal extension of the inflammatory process caused by ruptured follicles leads to papules, pustules, nodules, and cysts, which can lead to pitted or hypertrophic scarring. Figures 2-5 provide illustration of these common types of acne.

... DIFFERENTIAL DIAGNOSIS ...

Although the diagnosis of acne is often rather apparent, clinicians should be aware of exogenous

factors that may exacerbate acne or cause acneiform eruptions. Certain antiepilepsy medications and medications to treat bipolar disorder, such as phenytoin, carbamazepine, and lithium, can cause acneiform eruptions.¹³ Anabolic steroids as well as glucocorticoids can lead to folliculitis and acne that are fairly refractory to therapy unless these medications are stopped. Halides (iodides and bromides) as well as oral contraceptives containing high levels of progestins can also cause acneiform eruptions.¹⁴

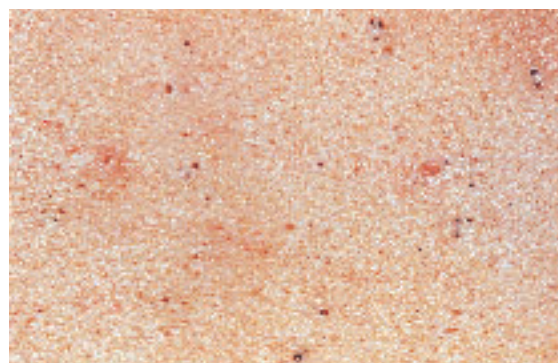
Acne rosacea can be distinguished from acne vulgaris by the former's association with flushing, telangiectasia, and rhinophyma. Generally, acne vulgaris is a disorder of adolescence and early adulthood, whereas acne rosacea is often seen in older populations.

Gram-negative bacterial folliculitis, commonly seen in immunocompromised patients or those receiving antibiotic therapy, may present with an outbreak of superficial pustules or papules. Follicular pustules can also be seen in infections caused by *Candida* or *Staphylococcus*. A bacterial culture or potassium hydroxide examination should be performed if this diagnosis is a possibility.

Perioral dermatitis, which is more commonly seen in women, is a condition in which papules and pustules on an erythematous background are seen on the nasolabial folds, chin, and upper lip. Potent topical corticosteroids and possibly cosmetics have been implicated as causes.

Acne may flare 2-7 days before menses or after sweating,¹⁵ and may be worsened by the application of cosmetics and oils. Diet plays little or no role in the development or worsening of acne, and contrary

Figure 1. Blackheads or Open Comedones



to common belief, chocolate has no role in the causation or worsening of acne.¹⁶ Patients should be told that acne is not caused by being “unclean” and that excessive scrubbing may exacerbate the condition.¹⁷

Acne conglobata is a highly inflammatory form of acne, with communicating cysts, abscesses, and the development of sinus tracts. It frequently results in pronounced scarring. Acne fulminans, a less common entity, is a form of extremely severe, ulcerative, cystic acne associated with fever, leukocytosis, and arthralgias.

... TOPICAL THERAPY ...

Topical therapy is the most appropriate first-line therapy for noninflammatory comedones or mildly inflammatory disease. The most frequently used topical agents include keratolytics, alpha-hydroxy acids, benzoyl peroxide, retinoid analogues, azelaic acid, and topical antibiotics. These agents, as well as cost data, are provided in the Table. Topical therapy avoids the possible systemic effects of oral medications.

Figure 2. Papular Acne



Figure 3. Papular Acne



Figure 4. Papulopustular Acne



Figure 5. Nodulocystic Acne



Keratolytics

Although once the mainstay of treatment of acne, keratolytics have been mostly supplanted by newer agents. However, they are available over the counter and still are used. These agents, which contain sulfur, resorcinol, or salicylic acid, either alone or in combination, are thought to exert their beneficial effects by causing sloughing of the epithelial cells in the lining of the follicle. They are available in non-prescription and prescription preparations and in various formulations: creams, lotions, gels, bar soaps, and liquid cleansers. Salicylic acid and other keratolytics are thought to be synergistic with benzoyl peroxide, but as single agents they are less comedolytic than benzoyl peroxide or tretinoin. Other disadvantages of keratolytics include the odor sometimes associated with hydrogen sulfide, brown scaling from resorcinol, and salicylism from excessive use of salicylates.¹⁴

Alpha-Hydroxy Acids

Alpha-hydroxy acids are organic acids derived mainly from fruit acids and used in the treatment of disorders associated with hyperkeratinization, such as xerosis, actinic damage, wrinkling, and acne. Commonly used agents include glycolic acid, which is derived from sugar cane; malic acid, which comes from apples; and citric acid, which is derived from citrus fruits. Cleopatra is said to have bathed in spoiled milk, which contains lactic acid, and women in the French

court are said to have washed their faces with spoiled wine, which contains tartaric acid.¹⁸ Alpha-hydroxy acids are available in several over-the-counter preparations in concentrations of 4% to 10% or through dermatologists or cosmetologists at higher concentrations.¹⁴

Though alpha-hydroxy acids do not seem to have antibacterial effects, they may cause decreased

Table. Costs of Some Topical Therapy for the Treatment of Acne*

Drug	Formulation	Average Wholesale Price
Benzoyl peroxide		
Generic (Consolidated Midland)	5% gel	\$2.25 (45 g)
	10% gel	\$2.50 (45 g)
Antibiotics		
Clindamycin		
<i>Cleocin T</i> (Upjohn)	1% gel (solution, lotion)	\$28.25 (30 g)
Erythromycin		
<i>Emgel</i> (Glaxo Wellcome)	2% gel	\$21.64 (27 g)
<i>Erycette</i> (Ortho)	2% solution	\$24.96 (60 swabs)
<i>T-Stat</i> (Westwood-Squibb)	2% solution	\$20.08 (60 mL)
		\$22.57 (60 pads)
Erythromycin/benzoyl peroxide		
<i>Benzamycin</i> (Dermik)	3%/5% gel	\$36.46 (23.3 g)
Azelaic acid		
<i>Azelex</i> (Allergan)	20% cream	\$33.75 (30 g)
Retinoids		
Tretinoin		
<i>Retin-A</i> (Ortho)	0.01% gel	\$26.88 (15 g)
	0.025% gel	\$27.12 (15 g)
	0.025% cream	\$30.78 (20 g)
	0.05% cream	\$34.56 (20 g)
	0.1% cream	\$40.32 (20 g)
	0.05% liquid	\$52.92 (28 mL)
<i>Avita</i> (Penederm)	0.025% cream	\$28.48 (20 g)
	0.025% gel	\$33.38 (20 g)
<i>Retin-A-Micro</i> (Ortho)	0.1% gel	\$33.96 (20 g)
Tazarotene		
<i>Tazorac</i> (Allergan)	0.05% gel	\$60.00 (30 g)
	0.1% gel	\$63.75 (30 g)
Adapalene		
<i>Differin</i> (Galderma)	0.1% gel	\$26.25 (15 g)
	0.1% solution	\$56.88 (30 mL)

*Source: 1999 Drug Topics Red Book. Montvale, NJ: Medical Economics Co; 1999.

keratinocyte cohesion, leading to increased desquamation.¹⁹ Therefore, the use of alpha-hydroxy acids might possibly prevent comedone formation. However, in a study comparing a topical alpha-hydroxy acid (gluconolactone in a 14% solution) to 5% benzoyl peroxide lotion in patients with mild to moderate inflammatory and noninflammatory acne lesions, the alpha-hydroxy acid was inferior to benzoyl peroxide at 8 and 12 weeks in reducing inflammatory lesions. No difference was appreciated between the agents regarding their ability to improve noninflammatory lesions. The alpha-hydroxy acids, however, were better tolerated than benzoyl peroxide.²⁰ Currently, there are not enough data to support the use of these agents over other agents for the treatment of acne.

Benzoyl Peroxide

Benzoyl peroxide is thought to exert its beneficial effects by suppressing the growth of *P acnes*, even more so than the topical antibiotics erythromycin or clindamycin.²¹ Benzoyl peroxide comes in various concentrations from 1% to 10% and in formulations of gels, lotions, creams, soaps, and washes and also can be purchased without a prescription. Interestingly, the antibacterial effects of lower strengths may be equivalent to those of the higher concentrations.²² The topical application of benzoyl peroxide has been shown to decrease counts of *P acnes* and to result in improvement in the treatment of both inflammatory and noninflammatory lesions.²³ When treatment is started, benzoyl peroxide can be applied every other day or daily, which can be increased to twice daily. Side effects include contact dermatitis and stinging, drying, and peeling, which can be minimized by a reduction in the dosage or the frequency of application. Benzoyl peroxide may lead to bleaching, and contact with hair or colored fabrics should be avoided. Benzoyl peroxide does not alter sebum production or composition and does not affect hyperkeratinization as well as other topical therapies.¹³

Retinoid Analogues

Analogues of retinoic acid (vitamin A acid) are one of the mainstays of therapy and are thought to exert their effects by reducing hyperkeratosis and decreasing the cohesiveness of follicular epithelial cells, thereby decreasing comedo formation.²⁴ Therapy with tretinoin (all-*trans* retinoic acid), thought to be one of the most effective topical comedolytic agents, is usually started at the lowest

strength preparation (0.025% cream); and the dosage is gradually increased, as tolerated, until eventually more efficacious formulations and stronger preparations are used.²⁵ One strategy would be to use the following sequence: 0.025% cream, 0.01% gel, 0.05% cream, 0.025% gel, 0.1% cream, 0.05% solution.²⁵ Efficacy depends not only on the concentration of the retinoid, but also on the type of formulation, with different formulations allowing for different levels of skin penetration.

Tretinoin can cause local irritation and drying; and because it may have a photoirritant effect, use of sunscreens may be necessary. A microsphere formulation of 0.1% tretinoin gel (Retin-A® Micro™, Ortho Dermatological, Skillman, NJ); and Avita® (Penederm Incorporated, Foster City, CA), another tretinoin product, may be less irritating.²⁶ Newer retinoid analogues, tazarotene and adapalene, are thought to be more specific for certain retinoic acid receptors, which may lead to fewer side effects. Tazarotene, available in 0.05% and 0.1% gels, has been shown to be more effective in the treatment of acne than its vehicle,²⁷ but it also causes erythema, burning, and stinging. Adapalene 0.1% gel has been shown to be less irritating than tretinoin 0.025% gel²⁸ and 0.025% cream.²⁹ It also has been shown to be more effective than tretinoin 0.025% gel in the treatment of noninflammatory acne lesions and as effective as tretinoin in the treatment of inflammatory lesions in patients with mild to moderate acne.³⁰ Maximal response to retinoids may not be seen for at least 12 weeks.³¹

Although teratogenicity is associated with systemic retinoid therapy, there is no evidence that topical retinoids lead to fetal abnormalities in humans. However, clinicians frequently discontinue topical retinoid therapy in pregnant patients.

Azelaic Acid

Azelaic acid, a dicarboxylic acid, is also useful in the topical treatment of acne. Besides being mildly comedolytic, it has activity against *P acnes* and inhibits melanocytic proliferation. This latter property may be helpful in darkly pigmented individuals, who often develop postinflammatory hyperpigmentation after the original lesion resolves.³² Azelaic acid was more effective than its placebo vehicle in resolving papules and pustules in patients with inflammatory acne and was as effective as 0.05% tretinoin cream in the treatment of noninflammatory lesions in patients with comedonal acne.³³

Topical Antibiotics

Because *P acnes* is thought to play a significant role in the pathogenesis of acne, topical antibiotics have been used successfully in its treatment and are thought to avoid some of the systemic side effects of their oral counterparts. In addition to reducing the counts of *P acnes*, topical antibiotics decrease the percentage of free fatty acids in surface lipids.¹³ Topical clindamycin and erythromycin are the most commonly used agents and have been shown to be superior to topical tetracycline³⁴ and effective in reducing the number of papules and pustules in patients with inflammatory acne.^{35,36} Although topical antibiotics have a defined role in the treatment of inflammatory acne, 2 studies have demonstrated that topical erythromycin or clindamycin is inferior to benzoyl peroxide when used in the treatment of non-inflammatory lesions.^{36,37} Concern has arisen that continuous use of topical antibiotics may induce resistant strains of *P acnes*.³¹ Resistance to topical erythromycin has emerged and may be of importance in treatment-refractory patients.

Topical erythromycin and clindamycin are both applied twice daily and can cause erythema, dryness, burning, and itching.

Combination Therapies

In order to take advantage of their different mechanisms of actions, various combinations of topical therapies have been used and have proven to be more efficacious than monotherapy. Sequential use of benzoyl peroxide and tretinoin (applying one in the morning and the other in the evening) has been shown to be more effective than use of either agent as monotherapy.^{38,39}

The combination of topical clindamycin and tretinoin is more effective than clindamycin monotherapy and was shown to reduce pustules by 60% and papules by 52% after 8 weeks of treatment.⁴⁰ Topical erythromycin and tretinoin combination therapy is another effective combination.

Benzoyl peroxide in combination with topical erythromycin has been shown to reduce *P acnes* resistance to the antibiotic, and the combination is superior to either agent alone.⁴¹

Role of Various Formulations

There are many commercial formulations of the various topical therapies, and one's choice of vehicle should be based on the patient's skin type and preference. In general, solutions and gels are drying and nongreasy and are best for patients with oily skin. Solutions often are helpful when large areas are

involved. Creams and lotions are more moisturizing and are often preferred by patients. Medication should be applied to areas of involvement, not specific lesions.

... ORAL ANTIBIOTICS ...

For patients refractory to topical therapy or those with more severe or extensive disease, oral antibiotics have been proven useful. Tetracyclines, erythromycin, trimethoprim, and trimethoprim/sulfamethoxazole have all been used to inhibit *P acnes*. Tetracycline and erythromycin also have an anti-inflammatory effect in vitro by decreasing neutrophil chemotaxis and chemotactic factors.¹⁴

Because of its low cost, tetracycline is often the oral antibiotic of choice for initial therapy and is started at 500 mg twice daily for 3-6 weeks, depending on response, and then reduced to 250 mg twice daily. Patients may be maintained on this reduced dose or switched to topical therapy. When patients don't respond adequately to tetracycline, doxycycline or minocycline can be tried and are frequently successful. Both are administered at a dosage of 50-100 mg twice daily, which is tapered after 3-6 weeks when the patient exhibits improvement. Minocycline is significantly more expensive than generic tetracycline or doxycycline and may be associated with an increased frequency of serious adverse events.⁴² Common adverse drug reactions attributed to tetracyclines include nausea, vomiting, diarrhea, vaginal candidiasis, photosensitivity, drug rashes, and hypersensitivity reactions. Tetracyclines should be avoided in pregnancy, during lactation, and in children younger than 9 years of age because of the risk of permanent tooth discoloration. Because minocycline is more lipophilic, it can cross the blood-brain barrier and may cause central nervous system effects such as headache, vertigo, ataxia, and light-headedness. Because the absorption of tetracycline is inhibited by food and dairy products, it should be taken on an empty stomach. Due to better absorption, doxycycline and minocycline can be taken with meals, which decreases the amount of gastrointestinal upset.

Though oral erythromycin used at a dosage of 500-1000 mg per day can be useful, both the development of bacterial resistance and gastrointestinal side effects (eg, nausea, vomiting, abdominal cramping, diarrhea) have limited its use. Trimethoprim/sulfamethoxazole can be used for patients refractory to oral tetracycline and erythromycin²² and is inexpensive. A variety of adverse

effects can occur, ranging in severity from mild gastrointestinal effects and allergic skin reactions to anaphylactoid reactions, hepatitis, pancreatitis, bone marrow suppression, renal impairment, and severe exfoliative skin reactions. Trimethoprim alone, which is thought to be the safer of the 2 components, can be used for patients resistant to other oral antibiotics.⁴³ It is generally given at a dosage of 300 mg twice daily when used in refractory patients; when used as an alternative antibiotic, it can be given at a dosage of 100 mg three times daily for 4-6 weeks and then reduced to 100 mg daily. Both trimethoprim/sulfamethoxazole and trimethoprim are contraindicated during pregnancy and lactation.

Although oral clindamycin has been shown to be effective in the treatment of inflammatory acne,⁴⁴ its association with pseudomembranous colitis has markedly diminished its role in treatment.

Maximal clinical benefit with oral antibiotics may not be seen for 3-4 months, and therapy is generally continued for 4-6 months. When patients don't respond to or worsen while receiving oral antibiotics, antibiotic resistance or the possibility of gram-negative folliculitis should be considered.

... ISOTRETINOIN ...

Patients with severe acne are frequently treated with oral isotretinoin (13-*cis*-retinoic acid), often with dramatic results. Isotretinoin is an ideal medication based on its mechanisms of action, which include a reduction in sebum production, inhibition of comedo formation, and a modulation of the inflammatory response³²; a course of therapy may lead to prolonged remission, even in the most severe cases.⁴⁵ In long-term follow-up, as many as 60% of patients may remain free of acne after a single course of therapy.⁴⁶

Doses of 0.1 mg/kg, 0.5 mg/kg, and 1.0 mg/kg result in similar degrees of improvement, but the higher dose is associated with a lower rate of relapse when therapy is discontinued in patients with nodular acne.⁴⁵ Therapy is generally started at lower doses and increased as tolerated until higher doses are reached and is continued for 20 weeks⁴⁷; the goal should be a minimum total dose of 120 mg/kg.⁴⁸ Even after the completion of a course of isotretinoin, improvement may continue for an additional 4-5 months; clinicians should therefore allow this amount of time to pass before initiating another course of treatment. Patients receiving a second course of isotretinoin frequently respond better than they did after their

first course,²⁵ although at times higher doses of isotretinoin (1.5 to 2.0 mg/kg daily) are required.⁴⁹

Unfortunately, isotretinoin is associated with a wide array of adverse effects, and only practitioners who are experienced with its use should prescribe it. It may cause arthralgias, stiffness, tendonitis, serum lipid abnormalities, alopecia, photosensitivity, mucosal and skin dryness, liver function test abnormalities, pancreatitis, depression, anemia, and leukopenia. Laboratory testing—including serum cholesterol, triglycerides, and high-density lipoprotein, liver function tests, and a complete blood count—should be performed before the initiation of isotretinoin therapy and periodically during the course of treatment, generally every 4-6 weeks.²⁵

Of particular concern is the risk to pregnant women, as isotretinoin is associated with spontaneous abortion and congenital malformations. Its teratogenicity mandates that appropriate screening and counseling be conducted before initiating therapy in women of childbearing age. Urine or serum pregnancy tests should be performed in the week before starting therapy and should be done monthly throughout treatment. Use of two methods of birth control is recommended; contraception should be practiced from 1 month before starting therapy until 1 month after it is discontinued.

A 16- to 20-week course of isotretinoin costs approximately \$500 to \$700.⁴⁹ Despite a paucity of large, randomized, controlled trials, isotretinoin (even with its higher medication costs) might be a more cost-effective alternative than continuous oral therapy with minocycline because of its greater efficacy.⁵⁰

... HORMONAL THERAPIES ...

In the subset of female patients with late-onset acne associated with signs of androgen excess, such as hirsutism and menstrual abnormalities, hormonal therapy with oral contraceptives or spironolactone may be considered. These agents are thought to work by decreasing androgen-induced sebum production. Of the oral contraceptives, those containing progestins of low androgenic activity are preferred. Norgestimate plus ethinyl estradiol (Ortho Tri-Cyclen; Ortho, Raritan, NJ) has been approved by the Food and Drug Administration for the treatment of acne. In a study of 257 women with moderate acne, 94% improved with this treatment versus 65% with placebo.⁵¹ Similarly, Redmond et al found that in a study of 250 women aged 15-49 years with moderate acne, there was a 51% reduction in inflam-

matory lesions and a 46% reduction in total lesions in the treatment group compared with a 34% reduction in both inflammatory and total lesions in the placebo group.⁵² According to the investigators' global assessment, there was an 83% improvement in patients using oral contraceptives and a 63% improvement in the subjects taking placebo. Additionally, the group taking oral contraceptives had a decrease in serum testosterone levels and an increase in sex hormone-binding globulin. Although oral contraceptives are beneficial in the treatment of acne, it may take up to 4 months of therapy for maximal benefit to be achieved.⁵³ If the diagnosis of hyperandrogenism is entertained, serum dehydroepiandrosterone sulfate or testosterone levels should be obtained. Low-dose prednisone, 5 mg or less, also can be used for those women with elevated dehydroepiandrosterone sulfate levels, which indicate adrenal androgen overproduction,¹⁴ and those with 11- or 21-hydroxylase block.⁵⁴

... OTHER THERAPIES ...

A variety of other therapies exist for the treatment of acne or acne-related scarring and are often used as adjuncts to medical therapy. Comedone extraction, performed by an experienced operator using a comedone extractor, can lead to more rapid improvement than topical therapy alone. Because improper placement of the comedone extractor may push the inflammatory material deeper in the skin and worsen the disease, it is inadvisable for patients to perform this procedure on themselves.

Intralesional corticosteroid injections can be used for large pustular nodulocystic lesions. Typically, this procedure involves the injection of 0.05-0.25 mL per lesion of a triamcinolone acetate suspension (2.5-10 mg/mL). This form of therapy can lead to rapid improvement.⁵⁵ Patients should be cautioned that intralesional corticosteroid therapy can lead to skin depression, which generally resolves in 4-6 months, but may be permanent. Therapy often has to be repeated every 2-3 weeks.

Patients with acne scarring can be referred to practitioners experienced in dermabrasion, laser resurfacing, punch grafts, collagen injections, or chemical peeling with trichloroacetic acid, alpha- or beta-hydroxy acids, or Jessner's solution (a solution containing the keratolytics resorcinol and salicylic acid, as well as lactic acid and ethanol).

... TREATMENT STRATEGIES BASED ON ACNE SUBTYPES ...

Comedonal Acne

Comedonal acne, most commonly seen in preteens and adolescents, is caused by increased sebum production and follicular plugging. Because inflammation has not yet occurred, therapy is directed at the prevention of new comedones and the establishment of an environment inhospitable to *P. acnes*. Topical retinoid analogues (eg, tretinoin, adapalene) would be the treatment of choice; salicylic acid is an acceptable alternative.

Mild Inflammatory Acne

After *P. acnes* proliferation within the occluded follicle, patients may develop mild inflammatory acne, manifested by scattered small pustules and papules. Topical antibiotics, benzoyl peroxide, or a combination of benzoyl peroxide and erythromycin are appropriate therapies.

Inflammatory Acne

Patients with more severe inflammation should be treated with the combination of a topical retinoid and either topical or oral antibiotics. When topical erythromycin is used, the addition of benzoyl peroxide should be considered. Because it takes 4-6 weeks to reduce proliferation of *P. acnes*, it may take this long before the cessation of new lesions; antibiotic dosages are usually maintained for 2-4 months.⁸

Although patients with nodular cystic acne may respond to oral antibiotics or the combination of oral antibiotics and topical therapy, those that don't should be considered for referral to someone experienced with the use of isotretinoin.

... CONCLUSION ...

Though not life threatening, acne can have severe psychological consequences and can severely impact the quality of life of affected patients. Additionally, with long-term complications such as scarring, patients may suffer with the stigmata of acne for a lifetime. A variety of therapies are available in our armamentarium that can alter the course of this disease. For severe, refractory disease, isotretinoin can be extremely useful, but should only be prescribed by physicians experienced with its use and its toxicity. Primary care and other providers should be aware of the many therapies available to treat patients with acne.

... REFERENCES ...

1. Kraning KK, Odland GF. Prevalence, morbidity, and cost of dermatologic diseases. *J Invest Dermatol* 1979;73:S395-S401.
2. Bergfeld WF. The evaluation and management of acne: Economic considerations. *J Am Acad Dermatol* 1995;32:S52-S56.
3. Ramsay DL, Fox AB. The ability of primary care physicians to recognize the common dermatoses. *Arch Dermatol* 1981;117:620-622.
4. Stern RS. Acne therapy: Medication use and sources of care in office-based practice. *Arch Dermatol* 1996;132:776-780.
5. Koo JY, Smith LL. Psychologic aspects of acne. *Pediatr Dermatol* 1991;8:185-188.
6. Cunliffe WJ. Acne and unemployment. *Br J Dermatol* 1986;115:386.
7. Pochi PE, Strauss JS. Endocrinologic control of the development and activity of the human sebaceous gland. *J Invest Dermatol* 1964;43:383-388.
8. Leyden JJ. Therapy for acne vulgaris. *New Engl J Med* 1997;336:1156-1162.
9. Rothman KF, Lucky AW. Acne vulgaris. *Adv Dermatol* 1993;8:347-374.
10. Leyden JJ, McGinley KJ, Mills OH, Kligman AM. Propionibacterium levels in patients with and without acne vulgaris. *J Invest Dermatol* 1975;65:382-384.
11. Puhvel SM, Sakamoto M. The chemoattractant properties of comedonal components. *J Invest Dermatol* 1978;71:324-329.
12. Shatila AR, Lee WL. Inflammatory acne. *Dermatol Clin* 1983;1:361-364.
13. Weiss JS. Current options for the topical treatment of acne vulgaris. *Pediatr Dermatol* 1997;14:480-488.
14. Taffe AM. Acne treatment: A comprehensive review of pharmacotherapy. *Lippincotts Prim Care Pract* 1997;1:790-787.
15. Cunliffe WJ, Cotterill JA. *The Acnes*. London, England: WB Saunders; 1975.
16. Fries JH. Chocolate: A review of published reports of allergic and other deleterious effects, real or presumed. *Ann Allergy* 1978;41:195-207.
17. Downing DT, Stewart ME, Wertz PW, Strauss JS. Essential fatty acids and acne. *J Am Acad Dermatol* 1986;14:221-225.
18. Clark CP III. Alpha hydroxy acids in skin care. *Clin Plast Surg* 1996;23:49-56.
19. Rubin MG. Therapeutics: Personal practice—the clinical use of alpha-hydroxy acids. *Australas J Dermatol* 1994;35:29-33.
20. Hunt MJ, Barnetson RS. A comparative study of gluconolactone versus benzoyl peroxide in the treatment of acne. *Australas J Dermatol* 1992;33:131-134.
21. Bladon PT, Burke BM, Cunliffe WJ, et al. Topical azelaic acid and the treatment of acne: A clinical and laboratory comparison with oral tetracycline. *Br J Dermatol* 1986;114:493-499.
22. Sykes NL, Webster GF. Acne: A review of the optimum treatment. *Drugs* 1994;48:59-70.
23. Cunliffe WJ, Holland KT. The effect of benzoyl peroxide on acne. *Acta Derm Venereol Suppl (Stockh)* 1980;61:267-269.
24. Berson DS, Shalita AR. The treatment of acne: The role of combination therapies. *J Am Acad Dermatol* 1995;32:S31-S41.
25. Brown SK, Shalita AR. Acne vulgaris. *Lancet* 1998;351:1871-1876.
26. DeGroot HE, Fallon Friedlander S. Update on acne. *Curr Opin Pediatr* 1998;10:381-386.
27. Gibson J. Rationale for the development of new topical treatments for acne vulgaris. *Cutis* 1996;57:S13-S19.
28. 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. *J Am Acad Dermatol* 1997;36:S126-S134.
29. Dunlap F, Mills O, Tuley M, et al. Adapalene 0.1% gel for the treatment of acne vulgaris: Superiority compared to tretinoin 0.025% cream in skin tolerance and patient preference. *Br J Dermatol* 1998;139:S17-S22.
30. 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.
31. Shalita AR. Topical acne therapy. *Dermatol Clin* 1983;1:399-403.
32. Webster GF. Acne and rosacea. *Med Clin North Am* 1998;82:1145-1154.
33. Cunliffe WJ, Holland KT. Clinical and laboratory studies on treatment with 20% azelaic acid cream for acne. *Acta Derm Venereol Suppl (Stockh)* 1989;133:S31-S34.
34. Eady EA, Holland KT, Cunliffe WJ. Should antibiotics be used for the treatment of acne vulgaris? *Br J Dermatol* 1982;107:235-246.
35. Tucker SB, Tausend R, Cochran R, Flannigan SA. Comparison of topical clindamycin phosphate, benzoyl peroxide, and a combination of the two for the treatment of acne vulgaris. *Br J Dermatol* 1984;110:487-492.
36. Burke B, Eady EA, Cunliffe WJ. Benzoyl peroxide versus topical erythromycin in the treatment of acne vulgaris. *Br J Dermatol* 1983;108:199-204.
37. Swinyer LJ, Baker MD, Swinyer TA, et al. A comparative study of benzoyl peroxide and clindamycin phosphate for treating acne vulgaris. *Br J Dermatol* 1988;119:615-622.
38. Fulton JE Jr, Farad-Bakeshandeh A, Bradley S. Studies on the mechanism of action of topical benzoyl peroxide and vitamin A acid in acne vulgaris. *J Cutan Pathol* 1974;1:191-200.
39. Hurwitz S. Acne vulgaris: Pathogenesis and management. *Pediatr Rev* 1994;15:47-52.
40. Rietschel R. Topical tretinoin in combination with topical clindamycin in the treatment of acne. *Fitzpatrick's J Clin Dermatol* September 1994:S13-S18.
41. Berson DS, Shalita AR. The treatment of acne: The role of combination therapies. *J Am Acad Dermatol* 1995;32:S31-S41.
42. Shapiro LE, Knowles SR, Shear NH. Comparative safety of tetracycline, minocycline, and doxycycline. *Arch Dermatol* 1997;133:1224-1230.
43. Bottomley WW, Cunliffe WJ. Oral trimethoprim as a third-line antibiotic in the management of acne vulgaris. *Dermatology* 1993;187:193-196.

44. Poulos ET, Tedesco FJ. Acne vulgaris: Double-blind trial comparing tetracycline and clindamycin. *Arch Dermatol* 1976;112:974-976.
45. Strauss JS, Rapini RP, Shalita AR, et al. Isotretinoin therapy for acne: Results of a multicenter dose-response study. *J Am Acad Dermatol* 1984;10:490-496.
46. Harns M, Masoye I, Radeff B. The relapses of cystic acne after isotretinoin treatment are age-related: A long-term follow-up study. *Dermatologica* 1986;172:148-153.
47. Shalita AR, Cunningham WJ, Leyden JJ, et al. Isotretinoin treatment of acne and related disorders: An update. *J Am Acad Dermatol* 1983;9:629-638.
48. Leyden JJ. The role of isotretinoin in the treatment of acne: Personal observations. *J Am Acad Dermatol* 1998;39:S45-S49.
49. Strasburger VC. Acne: What every pediatrician should know about treatment. *Pediatr Clin North Am* 1997;44:1505-1523.
50. Newton JN. How cost-effective is oral isotretinoin? *Dermatology* 1997;195:S10-S14.
51. Lucky AW, Henderson TA, Olson WH, et al. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. *J Am Acad Dermatol* 1997;37:746-754.
52. Redmond GP, Olson WH, Lippman JS, et al. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: A randomized placebo controlled trial. *Obstet Gynecol* 1997;89:615-622.
53. Kaul P, Coupey SM. Literature review: Hormonal therapy for acne in women. *J Pediatr Adolesc Gynecol* 1998;11:157-159.
54. Rose LI, Newmark SR, Strauss JS, Pochi PE. Adrenocortical hydroxylase deficiencies in acne vulgaris. *J Invest Dermatol* 1976;66:324-326.
55. Levine RM, Rasmussen JE. Intralesional corticosteroids in the treatment of nodulocystic acne. *Arch Dermatol* 1983;119:480-489.

CME QUESTIONS: TEST #060001

Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. Johns Hopkins University School of Medicine designates this continuing medical education activity for 1.0 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association. This CME activity was planned and produced in accordance with the ACCME Essentials and Standards for Commercial Support.

Instructions

After reading the article "Acne Vulgaris: Pathogenesis and Therapeutic Approach," select the best answer to each of the following questions. In order to receive 1 CME credit, at least 7 of the 10 answers must be correct. Estimated time for this activity is 1 hour. CME credits are distributed on a yearly basis.

1. True statements about acne include:

- a) acne is seen only during adolescence
- b) the annual cost of nonprescription drugs alone for acne is nearly \$100 million
- c) acne is rarely correctly diagnosed by primary care physicians
- d) visits to primary care providers for acne-related disorders actually decreased between 1980-1981 and 1989-1991

2. Patients suffering from acne vulgaris have been shown to:

- a) have poor self-esteem
- b) be less successful in gaining employment
- c) have social isolation
- d) all of the above

3. Which of the following statements regarding the pathogenesis of acne is *incorrect*?

- a) patients with acne exhibit hyper-responsiveness to endogenous androgens
- b) abnormal desquamation of epithelial cells in the follicle leads to follicular plugging
- c) *Propionibacterium acnes* is part of the normal flora of the skin and, contrary to common belief, has no role in the pathogenesis of acne
- d) free fatty acids and glycerol have proinflammatory and comedogenic properties

4. Which of the following is not associated with acneiform eruptions or the worsening of acne?

- a) carbamazepine
- b) lithium
- c) nifedipine
- d) halides

5. Which of the following statements are *false*?

- a) chocolate has repeatedly been shown to worsen acne
- b) dietary fats have not been shown to worsen acne
- c) acne is not caused by being "unclean"
- d) acne may flare before menses

6. True statements about benzoyl peroxide include:

- a) benzoyl peroxide does not suppress the growth of *Propionibacterium acnes*
- b) side effects include stinging, drying, and peeling
- c) unlike hydrogen peroxide, benzoyl peroxide does not bleach hair or colored fabrics
- d) all of the above

(CME QUESTIONS CONTINUE ON FOLLOWING PAGE)

CME TEST FORM

AJMC Test #060001

Acne Vulgaris:
Pathogenesis
and Therapeutic
Approach

(Test valid through
January 31, 2001.
No credit will be given
after this date.)

Please circle your answers:

- 1. a b c d
- 2. a b c d
- 3. a b c d
- 4. a b c d
- 5. a b c d
- 6. a b c d
- 7. a b c d
- 8. a b c d
- 9. a b
- 10. a b c d

(PLEASE PRINT CLEARLY)

Name _____

Address _____

City _____

State/ZIP _____

Phone # _____

Please enclose a check for \$10, payable to
American Medical Publishing, and mail with this form to:

The AJMC CME Test
American Medical Publishing
241 Forsgate Drive
Suite 102
Jamesburg, NJ 08831

PROGRAM EVALUATION

Johns Hopkins University School of Medicine appreciates your opinion on this article. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your CME test form. We thank you for your evaluation, which is most helpful in planning future programs.

On the whole, how do you rate the information presented in the article?

excellent good fair poor

Is the information presented useful in your practice?

yes no

Do you have recommendations to improve this program?

yes no

Comments:

Were any portions of this program unsatisfactory or inappropriate?

yes no

If so, which?

Do you find the information presented in these articles to be fair, objective, and balanced?

yes no

Is there subject matter you would like included in the future?

yes no

Comments:

In your opinion, were the authors biased in their discussion of any commercial product or service?

yes no

Comments:

Program Title

Physician Name

Address

City, State, ZIP

Specialty

(CME QUESTIONS CONTINUED FROM PREVIOUS PAGE)

7. True statements about topical therapy with retinoid analogues include:

- a) many studies have demonstrated that topical retinoids are teratogenic in humans, and clinicians must check urine or serum pregnancy tests before the initiation of therapy
- b) retinoid analogues are very effective anti-inflammatory agents; unfortunately they do not affect hyperkeratosis and do not decrease cohesiveness of follicular cells
- c) tretinoin may cause drying and local irritation
- d) newer retinoid analogues are less specific for retinoic acid receptors than their older counterparts

8. True statements about antibiotic therapy for acne include:

- a) topical tetracycline is clearly superior to topical erythromycin or topical clindamycin
- b) resistance to topical antibiotics has yet to be demonstrated

- c) topical erythromycin and clindamycin have a defined role in the treatment of inflammatory acne lesions
- d) all of the above

9. Tetracyclines, erythromycin, trimethoprim/sulfamethoxazole, and trimethoprim are all effective agents for the treatment of acne.

- a) true
- b) false

10. Which of the following statements about oral therapy with isotretinoin is correct?

- a) isotretinoin is teratogenic, and urine or serum pregnancy tests should be performed before starting therapy and monthly throughout treatment; female patients should use 2 methods of birth control
- b) isotretinoin use may cause hypertriglyceridemia
- c) only practitioners experienced with its use should prescribe isotretinoin
- d) all of the above