

# Diagnosis and Treatment of Acne

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Acne can cause significant embarrassment and anxiety in affected patients. It is important for family physicians to educate patients about available treatment options and their expected outcomes. Topical retinoids, benzoyl peroxide, sulfacetamide, and azelaic acid are effective in patients with mild or moderate comedones. Topical erythromycin or clindamycin can be added in patients with mild to moderate inflammatory acne or mixed acne. A six-month course of oral erythromycin, doxycycline, tetracycline, or minocycline can be used in patients with moderate to severe inflammatory acne. A low-androgen oral contraceptive pill is effective in women with moderate to severe acne. Isotretinoin is reserved for use in the treatment of the most severe or refractory cases of inflammatory acne. Because of its poor side effect profile and teratogenicity, isotretinoin (Accutane) must be prescribed by a physician who is a registered member of the manufacturer's System to Manage Accutane-Related Teratogenicity program. (Am Fam Physician 2004;69:2123-30, 2135-6. Copyright© 2004 American Academy of Family Physicians)

▶ A patient information handout on acne, written by the authors of this article, is provided on page 2135.

See page 2134 for levels of evidence definitions.

Acne is a disease of pilosebaceous units in the skin. It is thought to be caused by the interplay of four factors. Excessive sebum production secondary to sebaceous gland hyperplasia is the first abnormality to occur.<sup>1</sup> Subsequent hyperkeratinization of the hair follicle prevents normal shedding of the follicular keratinocytes, which then obstruct the follicle and form an inapparent microcomedo.<sup>2</sup> Lipids and cellular debris soon accumulate within the blocked follicle. This microenvironment encourages colonization of *Propionibacterium*

*acnes*, which provokes an immune response through the production of numerous inflammatory mediators. Inflammation is further enhanced by follicular rupture and subsequent leakage of lipids, bacteria, and fatty acids into the dermis.

## Diagnosis

The diagnosis of acne is based on the history and physical examination. Lesions most commonly develop in areas with the greatest concentration of sebaceous glands, which include the face, neck, chest, upper arms, and back.

Acne vulgaris may be defined as any disorder of the skin whose initial pathology is the microscopic microcomedo.<sup>3</sup> The microcomedo may evolve into visible open comedones ("blackheads") or closed comedones ("whiteheads"). Subsequently, inflammatory papules, pustules, and nodules may develop. Nodulocystic acne consists of pustular lesions larger than 0.5 cm. The presence of excoriations, postinflammatory hyperpigmentation, and scars should be noted.

Acne may be triggered or worsened by external factors such as mechanical obstruction (i.e., helmets, shirt collars), occupational exposures, or medications. Common medications that may cause or affect acne are listed in Table 1.<sup>4</sup> Cosmetics and emollients may occlude follicles and cause an acneiform

TABLE 1  
Medications that Trigger or Exacerbate Acne

### More commonly

Anabolic steroids (e.g., danazol [Danocrine], testosterone)  
Bromides  
Corticosteroids (e.g., prednisone [Deltasone])  
Corticotropin (H.P. Acthar)  
Isoniazid (Nydrazid)  
Lithium  
Phenytoin (Dilantin)

### Less commonly

Azathioprine (Imuran)  
Cyclosporine (Sandimmune, Neoral)  
Disulfiram (Antabuse)  
Phenobarbital  
Quinidine  
Tetracycline  
Vitamins B<sub>12</sub>, B<sub>6</sub>, B<sub>12</sub>, and D<sub>2</sub>

Adapted with permission from Zaenglein AL, Thiboutot DM. Acne vulgaris. In: Bologna JL, Jorizzo JJ, Rapini RP, eds. *Dermatology*. New York: Mosby, 2003:533-4.

eruption. Topical corticosteroids may produce perioral dermatitis, a localized erythematous papular or pustular eruption.<sup>5</sup>

Endocrine causes of acne include Cushing's disease or syndrome, polycystic ovary syndrome, and congenital adrenal hyperplasia.<sup>6</sup> Clinical clues to possible hyperandrogenism in women include dysmenorrhea, virilization (i.e., hirsutism, clitoromegaly, temporal balding), and severe acne.

### Classification

In 1990, the American Academy of Dermatology developed a classification scheme for primary acne vulgaris.<sup>7</sup> This grading scale delineates three levels of acne: mild, moderate, and severe. Mild acne is characterized by the presence of few to several papules and pustules, but no nodules (*Figure 1*). Patients with moderate acne have several to many papules and pustules, along with a few to several nodules (*Figure 2*). With severe acne, patients have numerous or extensive papules and pustules, as well as many nodules (*Figure 3*).

Acne also is classified by type of lesion—comedonal, papulopustular, and nodulocystic. Pustules and cysts are considered inflammatory acne.

### Therapy

#### TOPICAL AGENTS

Selection of topical therapy should be based on the severity and type of acne. Topical retinoids, benzoyl peroxide, and azelaic acid are effective treatments for mild acne. Topical antibiotics and medications with bacteriostatic and anti-inflammatory properties are effective for treating mild to moderate inflammatory acne. The dosage, approximate cost, and side effects of selected topical medications are summarized in *Table 2*.

Proper selection of topical formulations may decrease side effects and increase patient compliance. Fortunately, most acne medications are available in several forms. Creams and lotions typically are reserved for dry or sensitive skin, whereas gels are prescribed



FIGURE 1. Mild acne. This patient has a few erythematous papules and occasional pustules mixed with comedones.



FIGURE 2. Moderate acne. This patient has many erythematous papules and pustules, as well as prominent scarring.



FIGURE 3. Severe acne. This patient has extensive pustules, erythematous papules, and multiple deep-seated nodules within an extremely inflamed background.

**TABLE 2**  
**Selected Topical Medications for the Treatment of Acne**

Medication	Formulation	Cost* (quantity/weight)	Dosage	Side effects
<b>Retinoids</b>				
Adapalene (Differin)	Gel 0.1%	\$42 (15 g)	Once or twice daily, but can be once every other day if not well tolerated	Same as tretinoin but less severe
	Cream 0.1%	\$42 (15 g)		
	Pledget 0.1%	\$79 (60 count)		
	Solution 0.1%	\$79 (30 mL)		
Tazarotene (Tazorac)	Gel 0.05%	\$74 (30 g)	Once daily	Same as tretinoin but more severe
	Gel 0.1%	\$78 (30 g)		
	Cream 0.05%	\$74 (30 g)		
	Cream 0.1%	\$78 (30 g)		
Tretinoin (Retin-A)	Cream 0.025%	\$42 (20 g)	Once daily, but can use once every other day if not tolerated	Dryness, scaling, erythema, burning, irritation, and photosensitivity
	Cream 0.05%	\$47 (20 g)		
	Cream 0.1%	\$55 (20 g)		
	Gel 0.01%	\$33 (15 g)		
	Gel 0.025%	\$34 (15 g)		
	Solution 0.05%	\$71 (28 mL)		
Tretinoin microsphere (Retin-A Micro)	Gel 0.04%	\$42 (20 g)	Once daily, but can use once every other day if not tolerated	Dryness, scaling, erythema, burning, irritation, and photosensitivity
	Gel 0.1%	\$42 (20 g)		
<b>Antibiotics</b>				
Clindamycin (generic)	Gel 1%	\$32 (30 g)	Twice daily	Local irritation; stains clothes
	Lotion 1%	\$60 (60 mL)		
	Solution 1%	\$23 (30 mL)		
	Swab 1%	\$46 (60 swabs)		
Erythromycin	Gel 2%	\$18 (30 g)	Twice daily	Local irritation; stains clothes
	Solution 2%	\$8 (60 mL)		
<b>Other</b>				
Azelaic acid (Azelex)	Cream 20%	\$49 (30 g)	Twice daily	Dryness, scaling, erythema, burning, irritation, pruritus; rarely, hypopigmentation
Benzoyl peroxide (various)	Gel: 2.5%, 5%, or 10%	\$24 (90 g)	Once or twice daily	Erythema, peeling, contact dermatitis, dryness
	Wash: 2.5%, 5%, or 10%	\$25 to \$30 (227 mL)		
Sulfacetamide (Klaron)	Lotion 10%	\$104 (118 mL)	Twice daily	Itching, redness, irritation, and rare severe hypersensitivity reactions; contraindicated for those with sulfa allergies
Sulfacetamide/sulfur (Sulfacet-R)	Lotion 10%/5%	\$51 (25 g)	Twice daily	Same as sulfacetamide

\*—Average wholesale cost, based on Red Book, Montvale, N.J.: Medical Economics Data, 2003.

for oil-prone complexions. During treatment with prescribed medications, patients should use bland facial washes and moisturizers.

**Retinoids and Retinoid Analogs.** Topical tretinoin (Retin-A) is a comedolytic agent that normalizes desquamation of the epithelial lining, thereby preventing obstruction of the pilosebaceous outlet.<sup>8</sup> This agent also appears to have direct anti-inflammatory effects.<sup>9</sup> A

derivative of vitamin A, tretinoin is available in cream, gel, and liquid forms. In tretinoin microsphere (Retin-A Micro), tretinoin is encapsulated in a polymer that slowly releases the active medication, resulting in less irritation than with other tretinoin preparations.<sup>10</sup> With all retinoids, visible improvement occurs after eight to 12 weeks of treatment.

Tretinoin is inactivated by ultraviolet (UV)

light and oxidized by benzoyl peroxide. It therefore should be applied only at night and never with benzoyl peroxide. Tretinoin may decrease the amount of native UV protection by thinning the stratum corneum; thus, daily use of sunscreen is recommended. Because the irritation caused by tretinoin is dose-dependent, treatment should be initiated in a low dose. Patients only need a pea-sized amount of product per application.

There is no strong evidence for the teratogenicity of tretinoin, which remains pregnancy category C. A study<sup>11</sup> published in 1998 focused on the transdermal absorption of topical tretinoin and found the absorbed concentration to be below endogenous retinoid levels. However, no definitive consensus has been reached on the use of topical tretinoin in pregnancy. It may be wise to avoid use of topical retinoids or retinoid analogs in women who may become pregnant during treatment.

Adapalene (Differin) is a topical synthetic retinoid analog that normalizes differentiation of follicular epithelial cells and demonstrates direct anti-inflammatory properties. Double-blind studies have shown 0.1 percent adapalene gel to be as effective as 0.025 percent

tretinoin gel.<sup>12</sup> [Evidence level A, meta-analysis] Adapalene is superior to 0.025 percent tretinoin gel in both tolerability and speed of efficacy,<sup>12</sup> and is equivalent in efficacy to 0.1 percent tretinoin microsphere.<sup>13</sup> [Reference 13—Evidence level A, randomized controlled trial (RCT)] Adapalene is a reasonable choice as a first-line topical retinoid; this agent may be especially useful in patients who are unable to tolerate the irritation caused by tretinoin.

Tazarotene (Tazorac) is available in 0.05 and 0.1 percent gel and cream formulations. It is a pregnancy category X agent. Tazarotene may be more irritating than other retinoids. Dose-related erythema and burning are the most common adverse effects. Studies have indicated that tazarotene gel is a more efficacious keratolytic than tretinoin 0.025 percent gel<sup>14</sup> and tretinoin 0.1 percent microsphere gel.<sup>15</sup> Because tazarotene may increase irritation, it usually is considered a second-line retinoid option in patients who have not responded to topical tretinoin or adapalene therapy.

*Topical Antibiotics.* These agents are another mainstay of acne treatment. Topical antibiotics commonly are used in conjunction with retinoids or benzoyl peroxide in patients with any degree of inflammatory acne. The most frequently used topical antibiotics are clindamycin and erythromycin. These drugs normally are applied once or twice daily.

*Benzoyl Peroxide and Benzoyl Peroxide Combinations.* Benzoyl peroxide is inexpensive and available over the counter. It has a stronger effect on papules than tretinoin, but a weaker effect on comedones.<sup>16</sup> Combinations of topical antibiotics and benzoyl peroxide increase efficacy and reduce antibiotic resistance in patients with *P. acnes* colonization. The preparations are available in gel form, and include 1 percent clindamycin with 5 percent benzoyl peroxide (BenzaClin) and 3 percent erythromycin with 5 percent benzoyl peroxide (Benzamycin). The preparations are equally effective in the treatment of acne.<sup>17</sup> [Evidence level B, single blinded RCT] One study<sup>18</sup> comparing combined 1 percent clindamycin

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and 5 percent benzoyl peroxide with 1 percent clindamycin alone found the combination product to be more efficacious, with less *P. acnes* resistance. [Evidence level A, RCT]

**Azelaic Acid.** This agent is a dicarboxylic acid that has bacteriostatic and keratolytic properties. Azelaic acid (Azelex) may be particularly effective in the treatment of acne with postinflammatory hyperpigmentation.<sup>19</sup>

**Other Topical Agents.** Over-the-counter products may be used as primary or adjunctive treatments. Additional prescription topical agents include sulfacetamide (Klaron) and 10 percent sulfacetamide with 5 percent sulfur (Sulfacet-R). Sulfacetamide products are available in cream, gel, and wash formulations. These products generally are not considered first-line therapies, but they may be used in patients who cannot tolerate other topical agents.

#### SYSTEMIC AGENTS

**Oral Antibiotics.** When acne is resistant to topical therapies, oral antibiotics may be used. Oral antibiotics commonly are initial therapy in patients with moderate to severe inflammatory acne. Systemic antibiotics decrease *P. acnes* colonization and have intrinsic anti-inflammatory effects. First-line oral antibiotics have included tetracycline and erythromycin. Because *P. acnes* resistance to erythromycin is increasing, this antibiotic is becoming a second-line agent that is used when treatment with tetracycline or other macrolide antibiotics fails or is not tolerated.<sup>20</sup>

Tetracycline must be taken on an empty stomach. Iron supplements and milk products decrease systemic absorption of the antibiotic. Because of the risk of tooth discoloration and inhibited skeletal growth, tetracycline should not be used in pregnant women or children younger than nine years. Moderate to severe phototoxicity and gastrointestinal intolerance also may limit the use of tetracycline.

Doxycycline (e.g., Vibramycin, Doryx) frequently is used to treat moderate to severe acne vulgaris. However, associated photosen-

*Combinations of topical antibiotics and benzoyl peroxide increase efficacy and reduce antibiotic resistance in patients with Propionibacterium acnes colonization.*

sitivity may limit its usefulness.

Minocycline (Minocin) is a potent acne medication, but treatment with this antibiotic generally is reserved for patients who do not respond to or cannot tolerate aforementioned treatment options.<sup>21</sup> Rare but serious side effects are more common in patients taking minocycline than in patients treated with tetracycline or doxycycline.<sup>22</sup>

Oral antibiotics must be taken for six to eight weeks before results are evident, and treatment should be given for six months to prevent the development of microbial resistance.<sup>23</sup> Oral antibiotics may be discontinued after inflammation has resolved. Topical antibiotics may be continued for further treatment. Some patients may require long-term oral antibiotic therapy to control their acne and prevent scarring. The dosing, approximate cost, and side effects of systemic medication for the treatment of acne are summarized in *Table 3*.

**Oral Antibiotics and Oral Contraceptive Pills (OCPs).** A decrease in the effectiveness of OCPs is a concern with coadministration of oral antibiotics. Although this concern has not been supported by research, some package inserts contain a warning about decreased OCP efficacy with concomitant ampicillin or tetracycline therapy. A review of pharmacokinetic data showed a reduction of contraceptive steroid hormones only with concomitant use of rifampin (Rifadin).<sup>24</sup> [Evidence level B, nonquantitative systematic review] Nonetheless, it may be wise to inform patients receiving oral antibiotic therapy about the possibility of OCP failure, and to recommend the use of a second method of contraception.

OCPs. These contraceptives may be a valuable adjunct in the treatment of acne in female

patients. OCPs decrease circulating androgens, thereby decreasing sebum production.<sup>25</sup> The estrogen in OCPs increases the amount of sex hormone-binding globulin, which, in turn, decreases the free testosterone level. The estrogen also decreases secretion of gonadotropins by the anterior pituitary, with a consequent decrease in the amount of androgens produced by the ovaries. When an OCP is used to treat acne, the physician should prescribe a formulation that contains progestins with low androgenic possibility.<sup>25</sup> Appropriate

progestins include norethindrone (Norlutin), norethindrone acetate (Aygestin), ethynodiol diacetate (Zovia), and norgestimate (Ortho-Cyclen). Ultimately, the choice of OCP should be based on tolerability and compliance.

*Isotretinoin.* This vitamin A derivative is used to treat severe, often nodulocystic and inflammatory acne. Isotretinoin (Accutane) acts against the four pathogenic factors that contribute to acne. It is the only medication with the potential to suppress acne over the long term. To be able to prescribe this medica-

**TABLE 3**  
**Selected Systemic Medications for the Treatment of Acne**

Medication	Dosage	Cost* (quantity)	Side effects
Erythromycin stearate (Erythrocin)	250 mg twice daily	\$4 (30 tablets)	Nausea, vomiting, diarrhea, anorexia, abdominal pain and cramps, pruritus, rash, stomatitis, melena, elevated liver transaminase levels, jaundice, eosinophilia
Erythromycin base (generic)	500 mg twice daily 250 mg 500 mg	\$9 (30 tablets) \$8 (30 tablets)	
Doxycycline hyclate (Doryx)	50 mg twice daily	\$70 (30 capsules)	Dyspepsia, nausea, vomiting, anorexia, diarrhea, photosensitivity, stomatitis, discolored teeth (if patient is younger than eight years), esophagitis, lightheadedness, dizziness, vertigo, ataxia, headache, tinnitus, drowsiness, reported pseudotumor cerebri
	75 mg twice daily	\$75 (30 capsules)	
	100 mg twice daily	\$76 (30 capsules)	
Doxycycline (Vibramycin)	50 mg once or twice daily	\$75 (30 capsules)	
	100 mg once or twice daily	\$135 (30 capsules)	
Doxycycline (generic)	50 mg once or twice daily	\$22 (30 capsules)	
	100 mg once or twice daily	\$41 (30 capsules)	
Tetracycline (generic)	250 mg two to four times daily	\$8 (30 capsules)	Same as doxycycline
	500 mg two to four times daily	\$8 (30 capsules)	
Minocycline (Minocin)	50 mg once or twice daily	\$70 (30 capsules)	Same as doxycycline, plus rare lupus-like syndrome, or rare hypersensitivity reaction, and skin and mucous membrane hyperpigmentation
	100 mg once or twice daily	\$117 (30 capsules)	
Minocycline (generic)	50 mg once or twice daily	\$50 (30 capsules)	
	100 mg once or twice daily	\$100 (30 capsules)	
Isotretinoin (Accutane)	10 mg (Start 0.5 to 1 mg per kg per day; therapeutic range is 0.5 to 2 mg per kg per day divided in two doses for 15 to 20 weeks)	\$225 (30 capsules)	Common: cheilitis, dry skin and mucous membranes, pruritus, epistaxis, conjunctivitis, photosensitivity, arthralgia, hypertriglyceridemia, elevated liver transaminase levels, decreased night vision Rare: corneal opacities, pseudotumor cerebri, hyperostosis, hepatotoxicity, major birth defects, cataracts, premature epiphyseal closure, neutropenia, thrombocytopenia, reported cases of depression
	20 mg	\$280 (30 capsules)	
	40 mg	\$326 (30 capsules)	
	10 mg	\$219 (30 capsules)	
Isotretinoin (Amnesteem)	20 mg	\$260 (30 capsules)	
	40 mg	\$302 (30 capsules)	

\*—Average wholesale cost, based on Red Book, Montvale, N.J.: Medical Economics Data, 2003.

tion, the physician must be a registered member of the manufacturer's System to Manage Accutane-Related Teratogenicity (SMART) program. The SMART program was developed in conjunction with the U.S. Food and Drug Administration (FDA) to minimize unwanted pregnancies and educate patients about the possible severe adverse effects and teratogenicity of isotretinoin, which is a pregnancy category X drug.<sup>26</sup>

Hepatitis, hypertriglyceridemia, intracranial hypertension, arthralgia, myalgias, night blindness, and hyperostoses are rare side effects of isotretinoin therapy.<sup>27</sup> Serum liver function tests and triglyceride levels must be monitored monthly in patients receiving isotretinoin. When isotretinoin is present in the gestational period, it can result in severe fetal abnormalities involving several systems.<sup>27</sup> Therefore, two forms of contraception must be used during isotretinoin therapy and for one month after treatment has ended. To ensure that female patients are not pregnant when treatment is initiated, two negative urine pregnancy tests are required before isotretinoin is prescribed. Pregnancy status is rechecked at monthly visits.<sup>26</sup>

The link between isotretinoin and depression is controversial. A meta-analysis published in 2000 reviewed the purported risk of depression, suicide, or psychiatric disorders in patients taking isotretinoin and found no evidence that the drug was associated with an increased risk for depression, suicide, or other psychiatric disorders.<sup>28</sup> [Evidence level B, systematic review of cohort studies] However, several case reports<sup>28</sup> and case series<sup>28</sup> have described situations in which depression began on initiation of isotretinoin therapy.

### Goals of Therapy and Treatment of Complications

The goals of acne therapy include controlling acne lesions, preventing scarring, and minimizing morbidity. The family physician should be sensitive to issues related to medication compliance, the patient's personal goals

for acne treatment, and psychologic problems related to acne (e.g., anxiety). Lack of compliance, the most important cause of treatment failure, can be minimized by patient education and the establishment of realistic treatment goals.<sup>29</sup> The patient needs to know that the goal of treatment is to prevent new lesions. Current lesions must heal on their own. Visible improvement occurs after eight to 12 weeks of treatment.

Scarring always is a potential risk in inflammatory acne. The method of scar treatment depends largely on the morphology of the scar. Common treatments include resurfacing with ablative or nonablative lasers, dermabrasion, and chemical peels, although there is little evidence to support these options.<sup>30</sup> Soft tissue augmentation, undermining, and punch biopsy excision are additional alternatives.<sup>31</sup>

### Referral

The patient who has not responded to treatment as expected may need to be referred to a dermatologist. Gram-negative folliculitis should be suspected if inflammatory acne worsens after several months of oral antibiotic therapy. Acne fulminans is the rapid onset of severe, inflammatory acne, often accompanied by fever, arthralgia, and bone diathesis. The triad of severe acne, hidradenitis suppurativa, and dissecting cellulitis of the scalp may require aggressive treatment. Intralesional corticosteroid injections may benefit nodulocystic disease. If treatment with isotretinoin is indicated, the prescribing physician must be enrolled in the manufacturer's SMART program.

Referral also may be required because of treatment complications or for correction of scarring. In the future, treatment with blue or blue-red lasers may be readily available, and referral to the facilities that have these lasers may benefit patients with acne that does not improve with standard treatments.

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atane) in the treatment of psoriasis. He notes that he has not received funds for publishing articles on, or in promotion of, isotretinoin. Dr. Feldman also has received grant support from Galderma Laboratories, manufacturer of adapalene (Differin), and from Ortho Dermatological, manufacturer of tretinoin (Retin-A).

Figures 1 through 3 provided by Steven Feldman, M.D., Ph.D.

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