Acne
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I. BACKGROUND

Acne vulgaris is a common, chronic disorder, involving inflammation of the pilosebaceous units that can be varied in presentation and difficult to treat. Acne pathogenesis derives from four main factors: sebaceous gland hyperplasia, abnormal follicular desquamation, Propionibacterium acnes, and inflammation. The primary lesion is the microcomedo, which may evolve into a noninflammatory comedo (open or closed) or become inflamed and form a papule, pustule, or nodule (Figs. 1-1 and 1-2).

Most adolescents (80%) experience some acne; however, it may linger into adulthood. Lesions may begin as early as ages 8 to 10 years at adrenarche, when androgens of adrenal origin begin to stimulate pilosebaceous units. Severe disease affects boys 10 times more frequently than girls, and patients often have a family history of severe cystic acne (Fig. 1-3).

Neonatal acne or cephalic pustulosis is self-limited with an onset around 2 to 3 weeks of age. Nearly one in five newborns is affected by at least mild neonatal acne characterized by erythematous nonscarring papules on the face and neck, most commonly on the cheeks and nasal bridge. This disorder spontaneously resolves within 1 to 3 months. Malassezia spp. have been implicated in the pathogenesis of neonatal acne. Topical 2% ketoconazole cream as well as benzoyl peroxide (BPO) has been shown to be effective treatments, although parental reassurance alone is often sufficient, given the transient and benign nature of the eruption.

Infantile acne usually presents at 3 to 6 months of age and includes persistent comedones and inflammatory lesions with an increased risk of scarring. Immature infantile adrenal glands lead to elevated dehydroepiandrosterone (DHEAS) levels until the age of 12 months. Boys are more often affected than girls because of additional high testosterone levels between the ages of 6 and 12 months. Infantile acne usually resolves within 1 to 2 years; however, individuals with infantile acne may have an increased risk of severe acne as teenager’s acne. Acne in mid-childhood is relatively uncommon and may be a marker for adrenal or gonadal tumors. Further workup of these patients is advised.

Early-onset acne may be the first sign of an underlying hormonal abnormality, especially if there is an associated advanced bone age and early pubic hair development. At puberty, hormonal stimuli lead to increased growth and development of sebaceous follicles. Female patients with severe acne or evidence of virilization often have abnormally high levels of circulating androgens. Several studies have demonstrated that many female patients with milder forms of acne and no evidence of virilization may still have ovarian and/or adrenal overproduction of androgens. In those patients with normal circulating levels of androgens, there is some evidence that suggests a heightened end-organ responsiveness of the sebaceous glands to androgenic stimulation. This heightened end-organ response may result in increased conversion of testosterone to
dihydrotestosterone and other 5-α-reduced metabolites or suppressed follicular testosterone metabolism. Male acne patients tend to have higher levels of androstenedione, testosterone, free androgen index, and 11-deoxycortisol.1

As many as one-third of adult women are affected by a low-grade acneiform eruption that may start de novo or merge imperceptibly with preexisting adolescent acne. The eruption may be induced by chronic exposure to
comedogenic substances such as isopropyl myristate, cocoa butter, and fatty acids present in some creams and moisturizers, by androgenic stimuli from progestins present in some oral contraceptives, by recent cessation of oral contraceptives, or by unknown causes.

Inflammatory acne may yield both scarring and pigmentary changes. Early treatment is essential to prevent and minimize the cosmetic disfigurement associated with acne scarring. Adequate therapy will, in all cases, decrease its severity and may entirely suppress this disease.

II. CLINICAL PRESENTATION Acne has a significant impact on the patient’s self-image and quality of life, and the psychological toll of acne may be comparable to that of asthma or epilepsy. Even clinically mild acne may
cause considerable social embarrassment to the patient. As with all medical and psychological conditions, the patient's perception of the severity of the problem is an important factor in choosing treatment.

A. Noninflammatory Lesions. The initial lesion is the closed comedo; visible as a 1- to 2-mm white bump (whitehead) most easily seen when the skin is stretched. If follicle contents extrude, a 2- to 5-mm, dark-topped, open comedo (blackhead) results. Patients should be advised that this black material is simply oxidized keratin, not dirt.

B. Inflammatory Lesions. Erythematous papules, pustules, cysts, and abscesses may be seen. Patients with cystic acne also tend to show polyporous comedones, which result from prior inflammation during which epithelial scarring caused fistulous links between neighboring sebaceous units. Acne lesions are seen primarily on the face, but the neck, chest, shoulders, and back may be involved. One or more anatomic areas may be involved in any given patient, and the pattern of involvement, once present, tends to remain constant.

III. WORKUP Several points regarding etiology or therapy should be considered with each patient:

A. Endocrine Factors. Sudden onset of acne, treatment-resistant acne, and acne associated with signs of androgynism should lead one to suspect an endocrine abnormality.

1. Acne Accompanied by Irregular Menstrual Periods or Concomitant Hirsutism. Men and women with mild-to-severe cystic acne, especially those who do not respond to conventional therapy, may have elevated plasma-free testosterone and/or DHEAS levels. Hyperandrogenism is associated with acne, hirsutism, alopecia, and menstrual irregularities; other possible findings include infertility, deepening of the voice, increased libido, acanthosis nigricans, insulin resistance, type 2 diabetes mellitus, and dyslipidemia. DHEAS elevations above 8,000 ng/mL suggest the presence of an adrenal tumor; a range of 4,000 to 8,000 ng/mL is indicative of congenital adrenal hyperplasia. Testosterone elevations point to an ovarian dysfunction, with levels of 150 to 200 ng/dL suggesting an ovarian tumor. Oral contraceptives can mask an underlying endocrine disorder, so testing should be done 1 month after the discontinuation of exogenous hormones. Women may have high normal levels of DHEAS and testosterone and may benefit from hormonal therapy. Postmenopausal acne occurs in some women with previously oily skin, with the development of small closed comedones at the periphery of the face; unopposed adrenal androgens are the presumed cause. See Table 1-1.

2. Premenstrual Flare-Up. Premenstrual flares of acne are associated with a narrowing of the sebaceous duct orifice between days 15 and 20 of the menstrual cycle. This can lead to duct obstruction and resistance to the flow of sebum. Many women tend to do well on anovulatory drugs.

3. Acne Associated with Oral Contraceptives. Acne may be associated with oral contraceptive pills if recently started or discontinued and if composed of an androgenic progesterone. During the first two or three cycles
TABLE 1-1  Endocrinopathies to Consider in Patient with Acne

- Stein-Leventhal syndrome
- Cushing syndrome
- 21-Hydroxylase deficiency
- Polycystic ovarian syndrome (Fig. 1-4): defined by menstrual irregularities, acne, pelvic ultrasound imaging of subcapsular ovarian cysts, and an elevated luteinizing hormone to follicle-stimulating hormone ratio (a level greater than two to three is suggestive). The testosterone elevations are modest in the range of 80–150 ng/dL

Figure 1-4. Hirsutism related to polycystic ovary syndrome. This is the most common cause of androgen excess and hirsutism. Note the lesions of acne. (With permission from Goodheart HP. Goodheart’s Photoguide of Common Skin Disorders. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

on oral contraceptives, acne may worsen. Post-pill acne may continue for as long as a year after birth control pills are stopped. Although anovulatory drugs may provide excellent therapy for acne, the various pills differ enormously in their effect on the sebaceous gland. Oral contraceptives that contain the androgenic and antiestrogenic progestogens norgestrel and norethindrone acetate may actually provoke an acneiform eruption.

B. Acne due to Occupational or Chemical Exposure. Exposure to heavy oils, greases, polyvinyl chloride, chlorinated aromatic hydrocarbons, and tars can cause acne. These occlusive comedogenic agents will initiate lesions, as can some greasy substances used for hair care (pomade acne). Certain oily or greasy cosmetics and creams can also exacerbate acne.

C. Acne due to Occlusive Clothing or Habits. Mechanical trauma (pressure, friction, rubbing, and squeezing) from clothing or athletic wear or from behavioral habits will also cause lesions. For example, football players may develop acne lesions in the distribution of their helmet and chin strap.
D. Medications-Induced Acne. Drug-induced acne often presents as an abrupt, monomorphic eruption of inflammatory papules. The most prominent among these are corticosteroids, adrenocorticotropic hormone, phenytoin, androgens, anabolic steroids (danazol and testosterone), epidermal growth factor receptor inhibitors, and melanoma chemotherapy agents such as Vemurafenib. Other known stimuli include trimethadione, isoniazid, lithium, iodides, bromides, halothane, vitamin B₁₂, cobalt irradiation, and hyperalimentation therapy.

E. Rapid-Onset Acne Associated with Fever and Leukocytosis. Acne fulminans is a destructive arthropathy, resembling rheumatoid arthritis. SAPHO syndrome consists of synovitis, acne, pustulosis (palmar–plantar pustular psoriasis), hyperostoses, and osteitis; this is considered one of the spondyloarthropathies and has been reported with inflammatory bowel disease (IBD) and pyoderma gangrenosum. The PAPA syndrome, an autosomal dominant disorder, consists of pyogenic sterile arthritis, pyoderma gangrenosum, and acne.

F. Antibiotic-Resistant Acne. There is an increased incidence of bacterial resistance of both *P. acnes* and coagulase-negative *Staphylococcus aureus* noted after long-term antibiotic use. These resistant bacteria are found in both the patients and their close contacts. *Propionibacterium acnes* resistance to antibiotics should be considered in treatment failures. This is seen particularly with erythromycin; but cross-resistance can occur with clindamycin. Multiple antibiotics should not be used at the same time and BPOs should be added as a second agent to help minimize this possibility. The highest possible dose of an oral antibiotic should be started for as short a course as possible. Oral minocycline has the lowest risk of bacterial resistance over time. Oral isotretinoin reduces the total number of resistant *P. acnes*.

An unusual complication of chronic broad-spectrum antibiotic therapy is the development of a gram-negative folliculitis. Such patients will notice a sudden change in their acne, with the appearance of pustules or large inflammatory cysts that, on culture, usually grow *Proteus*, *Pseudomonas*, or *Klebsiella* species. Because acne cysts are sterile on routine bacteriologic culture, a sudden change in morphology warrants Gram stain and culture of cyst/abscess contents. This condition is treated with isotretinoin or the appropriate antibiotic determined from culture and sensitivity testing.

IV. TREATMENT Acne therapy must take into consideration a multitude of factors. Often multiple therapeutic agents are used simultaneously or on a rotation schedule depending on patient response and side effects. The treatment of acne is a dynamic process and must always include the patient’s subjective evaluation of his or her appearance and symptoms.

A. Topical Retinoids are the first-line treatment for acne and represent one of the most effective groups of drugs. A small percentage of patients may experience a pustular flare of their acne in the first few weeks of topical retinoid therapy, a transient effect that is indicative of the effectiveness of therapy. Tazarotene is labeled as category X, on the basis of its indication for psoriasis when larger areas with an altered skin barrier are treated. Tretinoin and adapalene are category C. Minimizing exposure to sunlight and sunlamps is advised with the use of all retinoids because of an increased susceptibility to burning, likely secondary to the thinning of the stratum
corneum. Patients should be given specific instructions on applying retinoids (Table 1-2).

1. **Tretinoin** (*trans*-retinoic acid; vitamin A acid) first became available 25 years ago. The irritant effects of tretinoin sometimes limit its usefulness, but these can be minimized by the correct method of application. Tretinoin increases epidermal cell turnover and decreases the cohesive-ness of cells, thereby inhibiting the formation of comedones while helping existing comedones to loosen and be expelled. Tretinoin also decreases the number of normal cell layers of the stratum corneum from 14 to 5. This decrease in the thickness of the barrier layer may potentiate the penetration of other topical agents.

2. **Adapalene** is a derivative of naphthoic acid and a selective retinoic acid analog. This product is not degraded by sunlight, is not phototoxic, and is compatible with BPO application at the same time. When compared with topical tretinoin 0.025% gel, there is a lower incidence of cutaneous irritation and it compares favorably in the reduction of both inflammatory and noninflammatory lesions. This effect may be secondary to its more selective binding, increased lipophilic properties, and follicular penetration. This is a good first-line therapy in colder climates or in patients with sensitive skin.

3. **Tazarotene** is a potent selective retinoid that binds to the retinoic acid receptors, RAR-β and RAR-γ. This drug is converted in the epidermis to its active metabolite tazarotenic acid and was originally developed

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**TABLE 1-2 Instructions for Retinoid Use**

The cream base is preferred for dry skin and the gels are preferred for oily skin. The strength of the product may be gradually increased once the patient has become tolerant of the weaker formulation.

- **a.** Apply sparingly every other night to the entire face except around the eyes, lips, and neck. After 2–3 wk, if no excess irritation, erythema, dryness, or scaling is noted, increase to every night. Tazarotene is best applied over or several minutes after the application of a moisturizer at bedtime.
- **b.** Use mild, gentle soaps not more than twice daily.
- **c.** Avoid excessive exposure to sun. Use sunscreens.
- **d.** Use water-based cosmetics if necessary.
- **e.** Expect mild redness and peeling within a week, lasting 3–4 wk, and a flare-up in the acne during the first 2–4 wk. This is explained to the patient as the surfacing of lesions onto the skin.
- **f.** Clearing requires approximately 3 mo. Inflammatory lesions improve more rapidly, but comedones take longer. Effectiveness cannot be judged before 8 wk and is best assessed at 12 wk.
- **g.** Continue retinoid application after the lesions clear.
- **h.** Apply less frequently if the daily use of the retinoid cannot be tolerated—for example, every other night or skipping every third night.
- **i.** Although there is negligible systemic absorption of topical retinoids, this agent should be discontinued if pregnancy is suspected. Cases of neurologic toxicity and ear malformation have been reported.
for the treatment of psoriasis. Tazorac is a category X drug and must be avoided in pregnancy. This drug can be irritating and should be avoided in patients with sensitive skin or seborrheic dermatitis. The 0.1% gel is more effective than the 0.05% concentration; however, starting with the 0.05% concentration may decrease the irritation. Some investigators advocate short-contact therapy, such as 1- to 5-minute exposures every other night, especially for patients with resistant comedones. Treatment time can be gradually increased to overnight. Twice-daily short-contact therapy can be tolerated in the individual with an oilier complexion. This product is not degraded by sunlight.

B. Topical Antimicrobials. Bacteriostatics can be applied twice daily to the point of mild dryness and erythema, but not discomfort.

1. **BPO** has a potent bacteriostatic effect with a reduction of *P. acnes* within 2 days and a reduction in lesion count after 4 days of application. BPO decreases the likelihood of bacterial resistance and should be a mainstay of every acne program, if tolerated. It is hypothesized that this agent is decomposed by the cysteine present in skin, after which free-radical oxygen is capable of oxidizing proteins in its vicinity. These proteins include the bacterial proteins of the sebaceous follicles, thereby decreasing the number of *P. acnes*. Contact sensitivity is observed in 1% to 3% of patients. BPO can bleach the color out of clothing. BPO products are now largely over the counter, with numerous brands available, varying in strength from 2.5% to 10%.

2. Topical Antibiotics may affect acne lesions by their bacteriostatic action or because of suppressive effects on the inflammatory response. Papular and pustular lesions respond best; the activity of comedonal or cystic acne may not be altered. Resistant organisms may emerge after continued therapy; combination therapy with BPO minimizes this risk. All topical antibiotics are applied twice daily.

   a. **Clindamycin Phosphate** is available in 1% concentration in a hydroalcoholic vehicle (30 or 60 mL) as a gel or lotion. There have been two reports of pseudomembranous colitis after topical use of clindamycin hydrochloride. Patients with IBD should avoid topical clindamycin use, and all patients should be warned to discontinue therapy if intestinal symptoms occur. Products that combine clindamycin with BPO include BenzaClin and Duac.

   b. **Erythromycin Base** applied topically has been a mainstay in treatment of acne. However, widespread resistance has now limited its use as a monotherapy. Its primary advantage lies in its safety in pregnant patients.

3. **Salicylic Acid** is a β-hydroxy acid that penetrates into the sebaceous gland and has comedolytic and anti-inflammatory properties. It can be used as an adjunctive therapy and is found in cleansers, toners, masks, and peels. Its side effects include erythema and scaling.

4. **Azelaic Acid** is a dicarboxylic acid that has antimicrobial, anti-inflammatory, and comedolytic activity, and it is relatively nonirritating. It is available as a cream (Azelex) or gel (Finacea) formulation. Azelaic acid may help lighten postinflammatory hyperpigmentation and is a good choice for ethnic or pigmented skin. It is not a photosensitizer and so far shows minimal tendency for bacterial resistance. This drug works best
when combined with other topical preparations, for example, BPOs and retinoids.

5. **Topical Dapsone** is useful in reducing inflammatory acne, although the exact mechanism is unknown. It should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency. Topical dapsone is pregnancy category C.

C. **Combination Therapy.** In combination therapy, the retinoid prevents or removes comedones, whereas BPO or topical antibiotic eradicates *P. acnes*. The retinoid also enhances absorption of the other product. Irritation reactions may limit the use of this combination therapy in some patients. Combinations may be composed of two or more separate single agents, or a branded combination product (Table 1-3).

D. **Systemic Antibiotics.** The beneficial effects of antibiotics are multifold. Not only are the number of bacteria and free fatty acid (FFA) levels decreased, but antibiotics useful in acne therapy also directly interfere with local chemical and cellular inflammatory mechanisms. Tetracycline, erythromycin, and clindamycin have been shown to inhibit leukocyte chemotaxis and other neutrophil inflammatory functions and may also directly inhibit extracellular lipases responsible for the generation of inflammatory compounds. Antibiotic therapy cannot be truly evaluated until 6 to 8 weeks after starting. Antibiotic levels in sebum are not detectable until approximately 7 days after treatment has started, and lipid formed in basal cells of sebaceous follicles may require 1 month to reach the skin surface. Although sebum composition changes, the rate of secretion remains constant; therefore, skin may remain oily. Therapy may need to be continued for several months. It is controversial whether to taper the oral antibiotics or to stop with no taper. Tapering may allow resistant organisms to grow more readily, while a sudden stop may lead to acne flare. Long-term use of antibiotics likely contributes to the pool of resistant organisms.

1. **Tetracycline Derivatives**
   a. **Minocycline** is overall the most effective antibiotic available to treat acne, but it can have serious side effects. This antibiotic is very lipid soluble and penetrates the sebaceous follicle more effectively; it is well absorbed, even with meals. Owing to its highly lipophilic nature, it crosses the blood–brain barrier and can precipitate pseudotumor cerebri syndrome. The duration of therapy can be a week to a year, with the most common presenting symptoms being headache, visual disturbances, diplopia, pulsatile tinnitus, nausea, and vomiting.
   
   Because minimal amounts of minocycline remain in the gut, the frequency of *Candida* vaginitis is less than in those taking tetracycline.

### TABLE 1-3 Examples of Branded Combination Topical Treatments

| 1. BPO and retinoid: Epiduo |
| 2. Retinoid and antibiotic: Veltin, Ziana |
| 3. BPO and antibiotic: Acanya, BenzaClin, Benzamycin, Duac |

BPO, benzoyl peroxide.
Most tetracycline-resistant bacteria are sensitive to minocycline at a dose of 100 mg b.i.d. Dizziness, nausea, and vomiting may be a problem if full doses are administered initially. Start at 50 mg/day and slowly increase to as much as 100 mg b.i.d. Some patients may eventually achieve complete control on 50 mg/day.

Minocycline may cause a blue discoloration of acne cysts or sites of trauma; this discoloration usually does not appear until 8 months of therapy with a total cumulative dose of 70 g and is usually reversibly after discontinuation of the drug, though resolution is exceedingly slow. Once a cumulative dose of 100 g is reached, alternative therapies should be considered. Cases of autoimmune hepatitis, serum sickness-like reactions, pulmonary infiltrates with eosinophilia, and a syndrome similar to drug-induced lupus have been reported secondary to minocycline. All symptoms resolve with discontinuation of the drug. The estimated risk is an 8.5-fold increase from controls, an absolute risk of 52.8 cases/100,000 prescriptions.2 If long-term minocycline is taken (i.e., >2 years), periodic liver function tests (LFTs) and antinuclear antibody levels may be warranted. A personal or family history of systemic lupus erythematosus or underlying liver and/or kidney disease may be relative contraindications to the use of this drug.

b. **Doxycycline** has similar absorption and duration-of-activity characteristics as minocycline. Its effectiveness in acne approaches that of minocycline, when used in the same manner with similar dosages. Early data suggest that subantimicrobial doses of doxycycline, 20 mg (Periostat), may play a therapeutic role in acne by reducing inflammation through anticollagenolytic, antimatrix-degrading metalloproteinase, and cytokine downregulating properties. Patients taking doxycycline must be warned to avoid excessive exposure to sunlight because of the photosensitivity that accompanies the use of this drug. Patients should be advised to take pills with food and a full glass of water, to avoid erosive esophagitis. The evening dose should be taken at least 30 minutes prior to lying down for bed. Patients who are unable to sit for at least 30 minutes are poor candidates for this medication. A history of gastric ulcers is also a relative contraindication.

2. **Erythromycin**, 1 g/day, is also effective in the treatment of acne. The same dose and time responses noted for tetracycline also apply for this drug. However, given up to 40% of *P. acnes* organisms are now resistant to erythromycin, combination with topical BPO may help decrease bacterial resistance. Elevated LFTs and reversible hepatotoxicity have infrequently been reported.

3. **Clindamycin**, 300 to 450 mg/day, is an effective agent for acne. However, the risk of pseudomembranous colitis limits its systemic use to only very severe cases that are unresponsive to all other modes of therapy.

4. **Trimethoprim–Sulfamethoxazole** has also been shown to decrease FFA levels and inhibit inflammatory acne. Trimethoprim is very lipophilic, which enhances follicle penetration. Start with one double-strength tablet at bedtime; up to two tablets per day may be used. A high rate of allergic reactions limits its use. Neutropenia may occur on long-term
therapy, and a baseline complete blood count with intermittent monitoring is recommended. Toxic epidermal necrolysis is unlikely to occur after the first month of therapy. Cases of hepatic necrosis and aplastic anemia have also been associated with this drug.

5. **Ampicillin** may also be helpful in certain patients. In resistant acne patients, culture may reveal gram-negative bacteria responsive to ampicillin.

6. **Azithromycin** in a 500-mg dose three times a week has been shown to yield a 60% reduction in inflammatory papules in 83% of patients enrolled in a 12-week study.3

E. **Sebaceous Gland Suppression**

1. **Oral Contraceptives** (estrogen given as an anovulatory agent) may be of use in unresponsive cases in young women after more conventional regimens have failed. If a patient with acne is already taking anovulatory agents for contraception, an effort should be made to use a formulation known to alleviate, rather than exacerbate, acne. Most or all the estrogen effect is the result of adrenal and androgen inhibition rather than local suppression at the gland site; small doses of androgen can overcome the sebum-suppressive effects of large doses of estrogen in women as well as in men. There is a direct correlation between the degree of sebaceous gland inhibition and acne improvement. The gland, however, responds variably to estrogen suppression. On average, there will be a decrease of 25% in sebum production on administration of 0.1 mg ethinyl estradiol. This drug and its 3-methyl ether, mestranol (which has two-thirds the potency of ethinyl estradiol), are the estrogens present in oral contraceptives. All combination birth control pills are antiandrogenic because they reduce free testosterone, testosterone conversion to 5-α-androstanediol, and sex hormone-binding globulin. With combination therapy, it is important to use a pill with adequate estrogenic effect linked with nonandrogenic progestosterones such as drospirenone, desogestrel, norgestimate, norethindrone, and ethynodiol diacetate. Drospirenone is a new progestogen with antimineralocorticoid, progestogenic, and antiandrogenic activity. Patients may exhibit a difference in the tolerability of side effects between the various progestational agents. If a patient has been taking an oral contraceptive with minimal side effects, the clinician does not need to change the pill unless there appears to be a correlation with worsening of acne.

The preferable pills are Yasmin (3 mg drospirenone and 0.03 mg ethinyl estradiol), Desogen and Ortho-Cept (0.15 mg desogestrel and 0.03 mg ethinyl estradiol), Ortho-Cyclen or Ortho Tri-Cyclen (0.25 mg norgestimate and 0.035 mg ethinyl estradiol), Alesse (0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol), Ovcon 35 (0.4 mg norethindrone and 0.035 mg ethinyl estradiol), Brevicon (0.5 mg norethindrone and 0.35 mg ethinyl estradiol), Modicon (0.5 mg norethindrone and 0.035 mg ethinyl estradiol), and Demulen (0.05 mg ethinyl estradiol and 1.0 mg ethynodiol diacetate), in decreasing order of effectiveness. Decrease in acne should be noted within 3 months and marked improvement should be noted within 4 months of administration. The progestational agents norgestrel and norethindrone acetate should be avoided (Ovral, Ovrette, Lo-Ovral, and Loestrin). Estrogen therapy is
rarely needed before age 16, after which time there will be no problem with growth retardation.

2. **Prednisone.** For individuals with an acute acne flare, prednisone can also be used in a dose of 20 mg/day for 1 week before an important occasion such as a wedding.

3. **Spirronolactone (Aldactone),** used for many years as a diuretic, is also an antiandrogen that blocks the binding of androgens to androgen receptors. It is useful in treating recalcitrant acne in women with adult acne. Menstrual irregularities and breast tenderness are common side effects, and the drug may be easier to use in women taking birth control pills. The drug should not be used during pregnancy, because it may block the normal development of male genitalia. Most clinicians recommend combined use of this drug with oral contraceptives. Spironolactone alters potassium excretion (usually only at higher doses and in only 10% of patients). Serum electrolytes should be monitored during initial institution of therapy. Nausea, vomiting, and anorexia are also common side effects.

Good candidates for this drug are individuals with a premenstrual flare-up of their acne, acne onset after the age of 25, oily skin, coexistent hirsutism, and acne that has a predilection for the lower face, especially the chin and mandible. Start patients on 50 to 100 mg/day taken with meals. If no clinical response is seen in 1 to 3 months, adjust the dose up to 200 mg/day if necessary. Once maintenance has been achieved, try to lower the dose to the lowest effective daily dose. Keep in mind that hirsutism requires higher doses and longer treatment schedules.

4. **Isotretinoin (13-cis-Retinoic Acid, Accutane)** should be considered for patients with severe recalcitrant cystic acne, or patients with evidence of scar formation. The beneficial effects of this synthetic retinoid are indisputable, although its mode of action remains unclear. Isotretinoin is sebostatic, inducing a decrease in sebum production rates to as low as 10% of pretreatment values. However, given that sebum production approaches pretreatment rates after therapy is completed without a concomitant return of acne, other mechanisms, such as an anti-inflammatory effect and correction of altered keratinization, may be equally important. Isotretinoin therapy causes a 2.6-fold decrease in androgen site-binding capacity.4

The initial dose of isotretinoin is 0.5 to 1.0 mg/kg of the patient’s body weight. The cumulative dose should be between 120 and 150 mg/kg, for optimal effectiveness and lasting results. This usually takes 5 to 6 months to achieve, depending on the daily dose the patient is able to tolerate. Although lower doses may achieve the same initial response rates, they are associated with a much higher recurrence rate on discontinuation of the drug.

In doses greater than 40 mg/day, the dose should be divided into morning and evening. Isotretinoin is fat soluble and absorption is enhanced by taking it with meals. Reports of treatment failure have been reported in patients taking concomitant anti-fat-absorbing medications or foods. Because the skin will often continue to clear after drug administration has been stopped, at least a 2-month waiting period and preferably a 6-month period is advised before one commits a patient to a second
course of therapy. Any woman who fails to respond to isotretinoin should be evaluated for hyperandrogenism. The response rate may be as high as 90% with one to two courses of treatment, and with adequate dosing, most patients experience prolonged remissions from their disease. In a 10-year follow-up study, 61% of patients were free from acne. Of those who relapsed, 23% required a second course. Ninety-six percent had relapsed within 3 years of therapy; truncal acne had a higher relapse rate.4

Intermittent isotretinoin at lower doses may benefit some patients with adult acne or stubborn isotretinoin treatment failures. In one study, with isotretinoin 0.5 mg/kg/day for 1 week every 4 weeks for a total of 6 months, the acne resolved in 88% of patients, and at 1 year, 39% had a relapse of their acne (73% relapse with truncal acne).4

Isotretinoin is teratogenic in humans. A pregnancy prevention program was initiated in 1988. Since that time, 0.3% of treated female patients have become pregnant; 38% of live born infants had retinoid embryopathic defects.

Women of childbearing age must have a negative pretreatment pregnancy test and continue adequate contraception for the duration of therapy. Because of the short half-life of isotretinoin, the current recommendation is that conception may be attempted 1 month after the cessation of treatment. Men may take isotretinoin without concern for its teratogenic effects. There has never been a report of retinoid embryopathic defects resulting from a man taking isotretinoin impregnating a female; however, patients are still advised not to take isotretinoin if they are actively trying to father a child. Both patients and physicians must register with the FDA-administered program iPLEDGE before starting the medication to minimize the risk associated with isotretinoin.

Other controversial and disputed associations include depression and IBD. The cases of depression may reflect an idiosyncratic response to the medication because larger, controlled studies have failed to find a causal association. Acne by itself can be associated with depression, but an increased awareness of this potential side effect of isotretinoin should be kept in mind before prescribing this drug and during follow-up. Recently, the association between IBD and isotretinoin has gained much attention from the media and has led to legal actions despite several studies suggesting no increased risk of IBD.5,6

Xerosis, cheilitis, alopecia, dry eyes, muscle and bone aches, and hypertriglyceridemia are frequent side effects, but all are reversible on discontinuation of therapy. Although patients may experience a temporary flare-up of their acne when treatment is started, this does not affect their ultimate response to isotretinoin. Excessive granulation tissue, giving a pyogenic granuloma-like picture, is a less common problem. Because of delayed or poor wound healing, elective surgery including attempts at cosmetic scar revision should be delayed for 6 months after the completion of isotretinoin therapy. Patients should also be advised to avoid laser treatment, hair-removal waxing, tattoos, and piercing.

F. Adjunctive Therapy

1. Intralesional Corticosteroids. The therapy of choice for cystic lesions and acne abscesses is the intralesional injection of small amounts of corticosteroid preparations (triamcinolone acetonide or diacetate, 0.63 to
2.5 mg/mL). The high local concentration of corticosteroid injected leads to rapid involution of these nonpyogenic, sterile, inflammatory lesions. Use of undiluted solutions or injections of too large an amount may lead to temporary atrophic depressions in the skin. Most lesions, particularly early ones, will flatten and disappear within 48 hours of injection.

2. Acne Surgery
   a. Comedo Expression. Gentle removal of comedones by pressing over the lesion with a comedo extractor not only relieves the patient of unsightly lesions but may also prevent progression to more inflammatory lesions. Occasionally, it may be necessary to incise the follicular opening carefully with a No. 11 scalpel blade or a 25-, 27-, or 30-gauge needle. Over-rigorous attempts to express comedones may result in an increased inflammatory response.

   Recurrence of comedones after removal is common. Open comedones have been shown to recur within 24 to 40 days and closed comedones, within 30 to 50 days. Fewer than 10% of comedo extractions are a complete success. Nevertheless, this mode of therapy, carefully done, is useful in the appropriate case.

   b. Draining of Cysts. Careful and judicious incision and drainage of cysts and/or abscesses may initiate healing and shorten the duration of lesions.

   c. Microdermabrasion, with aluminum oxide crystals or other abrasive substances, is advocated for treatment of acne and acne scars. Early data indicate that this modality may be a useful adjunct to other topical therapies.

3. Laser and Light Therapies
   a. Blue Light or Photodynamic Therapy (420 nm). These light sources cause an overproduction of porphyrins that are toxic to P. acnes. Pulsed green light (532 nm) is also approved for the treatment of acne and presumably works in the same way. Light treatments can be performed alone or with prior application of aminolevulinic acid 20% for 10 minutes to 2 hours. Protocols vary, but one standard treatment is every 3 weeks in a 3-month course. This may be performed in conjunction with other acne therapies.

   b. Nonablative Lasers in the Infrared Range rely on selective photothermolysis to target the follicle. Through transient thermal effects, P. acnes is reduced and sebaceous glands are heated and decreased in size. The 1,320-nm Nd:YAG, 1,450-nm diode, and 1,540-nm Er:glass lasers may be of some benefit in the treatment of inflammatory acne and clinical improvement in acne scars. Treatments are typically performed monthly for 4 to 6 months. Other therapies may be continued concomitantly. The limiting factors are patient discomfort and expense.

   c. Pulsed Dye Lasers in the Visible Light Range (585 to 595 nm) can be used to minimize erythema of active acne lesions and acne scars. However, data are inconsistent as to whether this laser decreases acne lesion counts.

   d. Broadband Intense Light and Vacuum (Acleara System; Isolaz). The latest tool uses broadband light to activate porphyrins to destroy P. acnes and reduce sebum production, while a vacuum
removes built-up sebaceous material and extracts comedones. Visible improvement is often appreciated in two to three treatments at 2-week intervals. Maintenance therapy may be performed every 4 to 6 weeks pending the progress.

4. α-Hydroxy Acids (Glycolic, Lactic, Pyruvic, and Citric Acids) and β-Hydroxy Acids (Salicylic Acid) are available in topical cream formulations or as peeling agents. Peels are applied in the physician office. These acids reduce corneocyte cohesion.

G. Acne scars

1. Laser Skin Resurfacing with ablative lasers in various wavelengths can improve the appearance of acne scars of all types but requires significant postoperative wound care and recovery time. Fractional resurfacing devices allow for remodeling acne scars through a series of treatments with less downtime. Nonablative lasers (see preceding text) are thought to stimulate collagen production and, thereby, gradually improve the appearance of pitted acne scars.

2. Dermabrasion Using High-Speed Diamond Buffing Drills can remove small and superficial scars and sometimes deep scars. However, this method is highly dependent on practitioner technique and can result in scarring in untrained hands.

3. Fillers. Fat transfer and injection of dermal filler substances can be used to elevate acne scars.

4. Surgical Techniques. Punch excision, punch elevation, and elliptical excision can be used to remove isolated ice-pick or deep boxcar scars.

H. Patient Education about Long-Standing Misconceptions

A number of myths circulate with regard to the relationship between habits, diet, hygiene, and acne. Patients should be counseled that if certain exposures aggravate their individual case of acne, these should be avoided. However, strict or fad diets and regimens are unlikely to affect sebaceous gland function or acne activity. Detailed information and instructions should be emphasized. Moreover, shared, realistic expectations between the physician and the patient of any acne treatment regimen or therapeutic approach are essential to achieve the desired improvement.

REFERENCES


