

CLINICAL PRACTICE

Acne

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 17-year-old boy with a six-month history of acne presents for initial evaluation and treatment. Physical examination reveals closed and open comedones and a large number of erythematous papules and pustules (50 or more) of the face and upper trunk. How should he be treated?

THE CLINICAL PROBLEM

Acne affects more than 85 percent of teenagers but frequently continues into adulthood.¹ Although there are more than 2 million visits to office-based physicians per year for patients in the age range of 15 to 19 years, the mean age at presentation for treatment is 24 years, with 10 percent of visits taking place when patients are between the ages of 35 and 44 years.² The social, psychological, and emotional impairment that can result from acne has been reported to be similar to that associated with epilepsy, asthma, diabetes, and arthritis.³ Patients evaluated at tertiary care centers are prone to depression, social withdrawal, anxiety, and anger and are more likely to be unemployed than persons without acne.^{4,5} Scarring can lead to lifelong problems in regard to self-esteem. The direct cost of acne in the United States is estimated to exceed \$1 billion per year, with \$100 million spent on over-the-counter acne products.⁶

Acne is a follicular disease, the principal abnormality of which is impaction and distention of the pilosebaceous unit. The cause of the hyperproliferation of keratinocytes and the abnormalities of differentiation and desquamation are unknown. It is likely that hyperresponsiveness to the stimulation of sebocytes and follicular keratinocytes by androgens leads to the hyperplasia of the sebaceous glands and the seborrhea that characterize acne.⁷⁻⁹

Propionibacterium acnes colonizes the follicular duct and proliferates in teenagers with acne.¹⁰ This organism probably contributes to the development of inflammation. With this combination of factors present, the follicular epithelium is invaded by lymphocytes; it ruptures, and sebum, microorganisms, and keratin are released into the dermis.¹¹ Neutrophils, lymphocytes, and foreign-body giant cells accumulate and produce the erythematous papules, pustules, and nodular swellings characteristic of inflammatory acne.

STRATEGIES AND EVIDENCE

DIAGNOSIS

The diagnosis of acne is usually readily made. Acne is characterized by open and closed comedones (blackheads and whiteheads), which are present either alone or, more commonly, with pustules and erythematous papules concentrated on the face and upper trunk. Many systems for grading the severity of disease have been used. The severity of acne is generally assessed by the number, type, and distribution of lesions.

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From a therapeutic standpoint, the presence of scarring may lead to a more aggressive approach than normally pursued. Table 1 gives a narrative description of acne, accompanied by representative photographs that illustrate a simplified classification of severity (Fig. 1 to 4).

THERAPY

Topical and oral agents for the treatment of acne are listed in Table 2.

Topical Treatment

Topical medications are active only where and when they are applied; their main action is the prevention of new lesions. Thus, they should be used daily on all areas of the skin that are prone to acne. Maintenance therapy is needed to prevent recurrence. The main side effect of topical products that limits their use is irritation; this is a consideration primarily for patients for whom multiple medications are prescribed and who use over-the-counter skin products. Patients should be discouraged from applying anything to the face other than what is recommended so that irritation may be avoided. Most of the topical preparations are available in a variety of strengths and delivery systems. Gels, pledgets, washes, and solutions are most drying and are particularly suited for oily skin, whereas creams, lotions, and ointments are preferable for patients with dry, easily irritated skin.



Figure 1. Mild Acne.
Multiple open and closed comedones are present, with few inflammatory papules.



Figure 2. Moderate Acne.
Erythematous papules and pustules are the predominant lesions, and disease is limited to the face.

Severity	Description
Mild	Comedones (noninflammatory lesions) are the main lesions. Papules and pustules (Fig. 1) may be present but are small and few in number (generally <10).
Moderate	Moderate numbers of papules and pustules (10–40) and comedones (10–40) are present (Fig. 2). Mild disease of the trunk may also be present.
Moderately severe	Numerous papules and pustules are present (40–100), usually with many comedones (40–100) and occasional larger, deeper nodular inflamed lesions (up to 5). Widespread affected areas usually involve the face, chest, and back (Fig. 3).
Severe	Nodulocystic acne and acne conglobata with many large, painful nodular or pustular lesions are present, along with many smaller papules, pustules, and comedones (Fig. 4A).

* The information is from Cunliffe et al.^{1,2}



Figure 3. Moderately Severe Acne.

Erythematous papules, pustules, and nodules are present on the face.

Topical Retinoids

Topical retinoids work to correct abnormalities in the follicular keratinocyte. They are effective in both the treatment and prevention of the primary lesion of acne, the comedo, and thereby limit the formation of inflammatory lesions.¹⁹ Some types also reduce inflammation by interfering with the interaction between toll-like receptor 2 and external products of *P. acnes* on the surface of antigen-presenting cells.²⁰ In addition, topical retinoids improve the penetration of other topical medications and may help to improve the hyperpigmentation that is left in dark skin types after the resolution of inflammatory lesions.^{21,22}

For the mild, primarily comedonal, types of acne (Fig. 1), topical retinoids may be used alone, where-



Figure 4. Severe Acne.

Multiple painful nodules are present on the back (Panel A) in spite of aggressive topical and oral interventions. (Similar lesions appear on the patient's chest and face.) Panel B shows the response after treatment with isotretinoin.

Table 2. Medications for the Treatment of Acne.

Drug	Dose	Side Effects	Other Considerations
Topical agents			
Retinoids			
Tretinoin	Applied once nightly; strengths of 0.025–0.1% available	Irritation (redness and scaling)	Generics available
Adapalene	Applied once daily, at night or in the morning	Minimal irritation ¹³	
Tazarotene*	Applied once nightly	Irritation	Limited data suggest tazarotene more effective than alternatives ^{14,15}
Antimicrobials			
Benzoyl peroxide, alone or with zinc, 2.5–10%	Applied once or twice daily	Benzoyl peroxide can bleach clothing and bedding	Available over the counter; 2.5–5% concentrations as effective as and less drying than 10% concentration
Clindamycin, erythromycin†	Applied once or twice daily	Propensity to resistance	Most effective for inflammatory lesions (rather than comedones); resistance a concern when used alone
Combination benzoyl peroxide and clindamycin or erythromycin	Applied once or twice daily		Combination more effective than topical antibiotics alone; limits development of resistance; use of individual products in combination less expensive and appears similarly effective ¹⁶
Other topical agents			
Azelaic acid, sodium sulfacetamide–sulfur, salicylic acid‡	Applied once or twice daily	Well tolerated	Good adjunctive or alternative treatments

as for patients with more severe acne, the use of these products in combination with topical or oral antimicrobial agents is appropriate.^{12,23} Randomized, double-blind, multicenter comparative studies have shown a reduction of 38 to 71 percent in noninflammatory and inflammatory lesion counts. Direct comparisons of topical retinoids have indicated that tazarotene in a 0.1 percent gel is more efficacious than 0.1 percent tretinoin or 0.1 percent adapalene,^{14,15} although tazarotene also tends to be the most irritating. The maximum therapeutic response to topical retinoids occurs over approximately 12 weeks.

Topical Antimicrobials

Topical antimicrobial agents are effective in the treatment of inflammatory disease.²⁴ Benzoyl peroxide is a bactericide and is an excellent first-line medication. The response to this agent is rapid, with improvement noted as early as five days after

treatment has begun, but irritation is common. Water-based products, as compared with alcohol-based products, when used at low peroxide concentrations (2.5 to 5 percent) will help to limit this problem and have an efficacy similar to that of other products in this class.²⁵

Topical clindamycin or erythromycin also may be useful, but, as documented in many randomized, clinical trials, these agents are most effective when used in combination with benzoyl peroxide or topical retinoids.^{16,26–28} Randomized trials have demonstrated a reduction in total lesion counts of 50 to 70 percent when combination therapy is used.^{16,26–28} Moreover, the topical antibiotics clindamycin and erythromycin rapidly induce bacterial resistance when used as monotherapy, and this resistance correlates with decreased clinical efficacy.^{29,30} Benzoyl peroxide does not induce resistance; when used with topical or oral antibiotics, it protects against the development of this problem,²⁹

Table 2. (Continued.)

Drug	Dose	Side Effects	Other Considerations
Oral antibiotics ‡			
Tetracycline§	250–500 mg once or twice daily	Gastrointestinal upset	Inexpensive; dosing limited by need to take on empty stomach
Doxycycline§	50–100 mg once or twice daily	Phototoxicity	20-mg dose antiinflammatory only; limited data on efficacy ¹⁷
Minocycline§	50–100 mg once or twice daily	Hyperpigmentation of teeth, oral mucosa, and skin; lupus-like reactions with long-term treatment	
Trimethoprim–sulfamethoxazole	One dose (160 mg trimethoprim, 800 mg sulfamethoxazole) twice daily	Toxic epidermal necrolysis and allergic eruptions	Trimethoprim may be used alone in 300-mg dose twice daily; limited data available ¹⁸
Erythromycin†	250–500 mg two to four times daily	Gastrointestinal upset	Resistance problematic; consensus is that efficacy is limited
Hormonal agents ¶			
Spirolactone§	50–200 mg in divided doses	Menstrual irregularities, breast tenderness	Higher doses more effective but cause more side effects; best given in combination with oral contraceptives
Estrogen-containing oral contraceptives	Daily	Potential side effects include thromboembolism	
Oral retinoid			
Isotretinoin	0.5–1.0 mg/kg/day in divided doses	Birth defects; adherence to pregnancy-prevention program outlined by drug manufacturer, including two initial negative pregnancy tests, is essential; hypertriglyceridemia, elevated results on liver-function tests, abnormal night vision, benign intracranial hypertension, dryness of the lips, ocular, nasal, and oral mucosa and skin, secondary staphylococcal infections, and arthralgias are possible common or important side effects; perform laboratory testing of lipid profiles and liver-function tests monthly until dose is stabilized	Relapse rate higher if patient is <16 yr at initial treatment, if acne is of high severity and involves the trunk, or if drug is used in adult women

* Tazarotene is in pregnancy category X: contraindicated in pregnancy.

† Clindamycin, erythromycin, and azelaic acid are in pregnancy category B: no evidence of risk in humans.

‡ Oral antibiotics are indicated for moderate-to-severe disease; for the treatment of acne on the chest, back, or shoulders; and in patients with inflammatory disease in whom topical combinations have failed or are not tolerated.

§ This drug is in pregnancy category D: positive evidence of risk in humans.

¶ Hormonal agents are for use in women only.

|| Isotretinoin is in pregnancy category X: contraindicated in pregnancy. It should be used only in patients with severe acne that does not clear with combined oral and topical therapy.

and its use has been recommended if treatment with antibiotics is continued for longer than three months. In a recent trial,¹⁶ the effects of benzoyl peroxide alone were similar to those of a more expensive combined benzoyl peroxide–erythromycin product. However, these comparators were used twice daily without the concomitant use of topical retinoids. There is no role for topical clindamycin or erythromycin if oral antibiotics are administered.

Other Topical Medications

Azelaic acid, products containing sodium sulfacetamide and sulfur, and salicylic acid preparations are generally well tolerated, but clinical experience indicates that they are less effective than the agents discussed above. Studies involving these products are few, and most have had limitations in their methods. These medications are best used as adjuncts or when other medications are not tolerated.

Finally, the avoidance of potentially irritating over-the-counter astringents, harsh cleansers, or antibacterial soaps should be emphasized.

ORAL THERAPY

Oral Antibiotics

Oral antibiotics are indicated for moderate-to-severe disease, for the treatment of acne on the chest, back, or shoulders, and in patients with inflammatory disease in whom topical combinations have failed or are not tolerated.

When oral therapy is warranted, tetracycline is inexpensive and often effective in previously untreated cases. Results from randomized clinical trials indicate that a 50 to 60 percent rate of improvement in inflammatory lesions can be expected.³¹ However, gastrointestinal side effects and the need to take tetracycline on an empty stomach are disadvantages. Clinical experience and limited data have suggested that doxycycline, minocycline, and trimethoprim-sulfamethoxazole are more effective than tetracycline.³²⁻³⁴ Doxycycline and minocycline are both preferred over trimethoprim-sulfamethoxazole because of the side-effect profile.

Starting the therapy at higher doses is recommended, since the response cannot be judged for at least six weeks and full efficacy is not apparent for three months. If little response is seen at six weeks, adjustments to the treatment plan such as adding topical medication or switching oral antibiotics are justified.

After control of the acne is achieved and maintained for at least two months, a reduction in the dose can be attempted. Oral antibiotic therapy generally is taken over a three-to-six-month course. Eventual discontinuance is the goal, followed by long-term topical therapy (typically with topical retinoids alone or in combination with benzoyl peroxide). Controversy exists as to the need for a second form of contraception in women using both oral contraceptives and oral antibiotics, but a panel of experts has recommended a conservative approach — i.e., two forms of contraception — given that individual patients show large decreases in plasma ethinyl estradiol levels when taking antibiotics, including tetracycline.³⁵

Lack of Response

Reasons that acne may have a poor response to treatment with antibiotics include inadequate potency (e.g., the use of topical therapy for severe disease), an inadequate duration of treatment (at least



Figure 5. Gram-Negative Folliculitis.

Pustules are centered around the anterior nares.

a month is needed to see a response), improper patient education, poor compliance with the use of medication, or the development of resistance to antibiotics.³⁶ Resistance is an increasing problem, since 60 percent of *P. acnes* isolates are resistant to at least one antibiotic; resistance is most common with the use of erythromycin (50 percent of cases), clindamycin (35 percent), and tetracycline (25 percent).^{36,37} Resistance to antibiotics should be suspected in patients who do not have a response to treatment or who have a relapse during treatment, especially those who have been on multiple courses of oral and topical antibiotics or have a history of variable compliance. Because resistance to erythromycin and clindamycin are often present simultaneously, the occurrence of a flare of acne while one of these antibiotics is being used should prompt a switch to tetracycline or doxycycline. Tetracycline-resistant strains of *P. acnes* are usually also resistant to doxycycline, so a switch to minocycline is recommended if resistance to tetracycline is suspected.³⁸ The implications associated with the development

of resistant organisms, including *Staphylococcus aureus* in the nares, streptococci in the oropharynx, and enterobacteria, are currently uncertain.³⁹

Infection with gram-negative organisms may also complicate long-term antibiotic therapy. The overgrowth of gram-negative organisms in the anterior nares has been reported to occur in 85 percent of patients treated with oral antibiotics for six months or longer.⁴⁰ In 4 percent of such patients, pustules may develop, primarily on the central and lower face (Fig. 5); a culture of one of the pustules will yield a gram-negative organism identical to that present in the anterior nares. Such superinfected acne is best treated with isotretinoin.⁴⁰

Hormonal Therapy

In women who have signs of hyperandrogenism (e.g., irregular menses, androgenic alopecia typified by decreased hair density from the vertex to the anterior scalp, or hirsutism), who have acne that is resistant to conventional therapy, who quickly have a relapse after a course of isotretinoin, or who have a sudden onset of severe acne, an evaluation for androgen excess is indicated; this should minimally include serum dehydroepiandrosterone and free testosterone levels.⁴¹ If these levels are elevated, further evaluation for specific disorders (e.g., virilizing tumors, congenital adrenal hyperplasia, or polycystic ovary syndrome) may allow for targeted therapies, although a discussion of these therapies is beyond the scope of this review.

Therapy with oral contraceptives containing estrogen or with spironolactone, an androgen antagonist, is often useful in women with hyperandrogenism and in women with normal serum androgen levels.⁴²⁻⁴⁷ Norgestimate-ethinyl estradiol (Ortho Tri-cyclen) and norethindrone acetate-ethinyl estradiol (Estrostep) are approved by the Food and Drug Administration for the treatment of acne, and studies indicate that drospirenone-ethinyl estradiol (Yasmin) and levonorgestrel-ethinyl estradiol (Alesse) are also effective. Studies generally indicate that after six to nine months of use, there is a reduction in inflammatory-lesion counts of 30 to 60 percent, with improvement occurring in 50 to 90 percent of patients.⁴³⁻⁴⁶ Any oral contraceptive that contains estrogen is likely to have similar positive effects. The effects on acne of injectable progestins and patch systems have not been evaluated, and progesterone-only contraceptives may make acne worse.

Clinical observation indicates that women with



Figure 6. Acne on the Lower Face of a Woman.

deep-seated nodules of the lower face and neck (Fig. 6) are part of a subset of patients in whom hormonal treatment may be especially useful.⁹ A response to hormonal intervention may be seen after one menstrual cycle, but three to six months are needed to judge the full effect. Usually, oral contraceptives are tried first; if these are ineffective after several months, spironolactone, 50 to 100 mg, is added. This sequence is sensible, since contraception is warranted when spironolactone is used, because of the potential teratogenic effects of this drug. Hormonal treatment is especially useful in women who desire contraception or have other manifestations of hyperandrogenism, such as irregular menstrual cycles or hirsutism. Oral antibiotics and topical therapy may be used in combination with hormonal treatments.^{48,49}

Isotretinoin

Patients with severe acne that does not clear with combined oral and topical therapy are candidates for treatment with oral isotretinoin. When the use of this agent is being considered, an assessment of the severity of disease should include the effect of the acne on the patient, such as the potential for scarring.⁵⁰ Isotretinoin reduces the size and secretions of sebaceous glands, secondarily inhibits the growth of *P. acnes* and the resulting inflammation, and prevents comedogenesis through normalization of the differentiation of follicular keratinocytes. Isotretinoin thus affects all four pathogenic factors of acne, which explains its nearly universal efficacy during active therapy.^{9,51} In addition, it is the only treatment that leads to remission that may be permanent.⁵²

Approximately 40 percent of patients remain free of acne after one course of treatment, 40 percent have a recurrence of low severity that responds to medications to which the acne had previously been

resistant, and 20 percent will need repeated treatment with isotretinoin at a future time.⁵³ Patients younger than 16 years, those with severe acne on the trunk, and adult women are more likely than others to have a relapse.^{52,54-57} These first two groups may require multiple courses of isotretinoin over the duration of their acne-prone years, whereas the third group is best treated with hormonal therapy. The chance of a prolonged remission is greater when a total dose of 120 to 150 mg per kilogram of body weight is achieved.⁵³ Most patients can be started on 20 to 40 mg per day, with an increase to 40 to 80 mg over several months. Side effects of therapy are dose-dependent and may be limited by treatment with reduced doses over an extended period.

Isotretinoin is teratogenic; embryopathy (including, characteristically, ear defects combined with either central nervous system defects, cardiovascular defects, or both) has been reported to be caused after a single dose. Women of childbearing age must closely follow the pregnancy-prevention program outlined by the drug's manufacturer. The psychological status of the patient should also be monitored carefully. Although population-based studies have not confirmed an association between the use of isotretinoin and the risk of suicide or depression,^{50,58,59} there have been case reports of depression that occurred in the first two months after the start of treatment, cleared after the cessation of therapy, and recurred with the resumption of therapy.⁶⁰ Acne is known to be associated with anxiety, depression, and a negative self-image, and successful treatment with isotretinoin improves these factors. Thus, the potential for depression or suicide that may accompany treatment with isotretinoin must be balanced with the psychological benefits of effective treatment.⁶¹

Isotretinoin may cause hypertriglyceridemia and, to a lesser extent, can affect cholesterol levels. Alterations in dosing or dietary interventions usually allow for the continuation of treatment. Drying of the nasal mucosa may occur, which can lead to col-

onization of *S. aureus*, the potential complications of which include abscesses, conjunctivitis, impetigo, cellulitis, and folliculitis. These complications may be prevented with the use of intranasal bacitracin.⁶²

Other Forms of Therapy

The physical removal of comedones and the direct injection of steroids into inflamed cysts are two techniques that have been clinically shown to result in the rapid relief of acne.⁶³ Other methods such as chemical peels, microdermabrasion, and treatment involving light, lasers, or radiofrequencies require more investigation in order to clarify their role in therapy.

AREAS OF UNCERTAINTY

Randomized, controlled trials are needed to define the relative efficacies of various therapies and to guide the optimal sequence of alternative therapies, with attention to long-term efficacy, quality of life, and costs.

GUIDELINES

There are currently no formal up-to-date, evidence-based guidelines available.

CONCLUSIONS AND RECOMMENDATIONS

The management of acne depends on its severity. For the patient in the vignette, in whom moderately severe acne is present (based on the large number of papules and pustules, and their distribution), I would prescribe both topical and oral therapy. For the face, I would initially prescribe 0.025 percent tretinoin for nighttime use, in combination with 5 percent benzoyl peroxide, in an aqueous vehicle, in the morning. I would also prescribe 500 mg of tetracycline twice daily. I would see the patient in six to eight weeks to assess efficacy, irritation, and compliance and to adjust the regimen accordingly.

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