

CLINICAL PRACTICE

Acne

William D. James, M.D.

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.

N ENGL J MED 352;14 WWW.NEJM.ORG APRIL 7, 2005

1463

The New England Journal of Medicine as published by New England Journal of Medicine.

Downloaded from www.nejm.org at ALLERGAN INC on August 10, 2010. For personal use only. No other uses without permission.

Copyright © 2005 Massachusetts Medical Society. All rights reserved.

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.

Table 1. Classification of Acne.*	
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.¹²



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.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.