CLINICAL PRACTICE

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Acne Vulgaris

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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 15-year-old girl presents with moderate acne vulgaris that has not responded to over-the-counter acne treatments, including salicylic acid and benzoyl peroxide. She has many closed comedones, inflammatory papules, and pustules over the cheeks, forehead, and chin and numerous small, inflammatory papules on the back and chest. The lesions heal, leaving prominent, hyperpigmented macules that last for months. She is very distressed by the acne. Her mother notes that her daughter is more withdrawn and did not try out for a school play because of concerns about her appearance. How would you evaluate and treat this patient?

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THE CLINICAL PROBLEM

Acne vulgaris is a common disorder of the pilosebaceous unit, affecting approximately 85% of persons 12 to 25 years of age in the United States.[1] Acne often persists into adulthood, with 26% of women and 12% of men reporting acne in their 40s.[2] Globally, acne ranks 8th in overall disease prevalence, with the highest rates reported in Western Europe, "high-income" North America, and southern Latin America.[3] Acne is typically categorized according to age and includes neonatal and childhood manifestations. In this article, only acne occurring in adolescents and adults is discussed.

The face is usually the first thing that is noticed about a person, and acne can negatively affect others' perceptions.[4] The psychological effects of acne can be profound, and persons with acne are at risk for substantial, negative effects on quality of life, similar to those seen in persons with asthma, epilepsy, or arthritis.[5] Adolescents and adults with acne have higher rates of anxiety, low self-worth, and depression than those without acne.[6] In addition, adults with severe acne have higher unemployment rates than age-matched controls without acne.[7] Risk factors for the development of acne include a family history of severe acne, the polycystic ovary syndrome (PCOS), the metabolic syndrome, and rare genetic conditions (e.g., Apert's syndrome).

Acne is a primary inflammatory disorder involving the pilosebaceous unit. The pathogenesis is multifactorial, involving four key factors with interrelated mechanisms: increased sebum production, hyperkeratinization of the follicular infundibulum, inflammation, and *Cutibacterium acnes* (formerly *Propionibacterium acnes*) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Studies involving twins have shown that acne is highly heritable, with 81% of the population variance attributed to genetic factors.[8] Sebum-excretion rates and the presence of acne have greater concordance among monozygotic twins than among dizygotic twins.[9]

An audio version of this article is available at NEJM.org

KEY CLINICAL POINTS

ACNE VULGARIS

- The negative psychological effect of acne vulgaris can be profound and long-lasting.
- Combination therapy with a retinoid and a benzoyl peroxide–containing antimicrobial agent is used to control mild-to-severe inflammatory acne.
- For moderate-to-severe cases, an oral antibiotic agent is also recommended, with the duration of use being typically limited to 3 to 4 months. Once clinical improvement occurs, acne control is maintained with a topical retinoid. Benzoyl peroxide may also be continued if needed.
- Combined oral contraceptive therapy and spironolactone are effective hormonal therapies for inflammatory acne in female patients and may be considered in patients who do not have a response to topical therapies alone.
- In patients with severe nodulocystic acne or with acne that is unresponsive to combination therapy, the use of isotretinoin should be considered. Because of teratogenicity, prescribers should be familiar with recommended pregnancy-prevention measures and monitoring guidelines and be registered in the iPLEDGE system (in the United States).

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

A diagnosis of acne is typically made by means of clinical evaluation. Patients should be asked about family history, symptoms, and signs that are suggestive of hyperandrogenism or another endocrine disorder, including cortisol or growth hormone excess. For example, a history of irregular menstrual periods and hirsutism is suggestive of PCOS, whereas a sudden onset of acne could be a sign of a gonadal tumor. Patients should also be queried about the use of medications that have been associated with acne (e.g., phenytoin, lithium, glucocorticoids, and progestin-only contraceptives). The use of exogenous androgens commonly results in acne flaring. In limited case series, whey protein supplements have been linked to the exacerbation of acne, particularly truncal acne.[10]

The primary lesion types in acne are comedones (open or closed) and inflammatory lesions (papules, pustules, and nodules). The typical distribution involves the sebaceous gland–rich areas of the face, upper back, chest, and shoulders. Secondary changes of scarring, postinflammatory hyperpigmentation, or erythema should be noted and will influence the management of acne.

Acne severity can vary widely, from mild to very severe fulminant disease (including isotretinoin-induced acne fulminans) with systemic involvement, including fever, arthralgias, and lytic bone lesions (Fig. 1). Treatment is based on the types of lesions as well as on their severity and distribution. Although no universal grading scale has been recognized, the documentation of severity (clear, almost clear, mild, moderate, or severe) guides treatment.

In patients with atypical, very severe, or recalcitrant acne, particularly with abrupt onset, and in female patients who have signs of androgen excess, laboratory and radiographic workup is indicated. If PCOS is suspected, serum total and free testosterone levels should be measured. Other laboratory testing (e.g., dehydroepiandrosterone sulfate, thyrotropin, cortisol, and serum 17-hydroxyprogesterone [to assess for late-onset congenital adrenal hyperplasia]) is limited to selected cases.

TREATMENT

Before a treatment plan is devised, it is vital to review the patient's skin care routine, including the frequency of washing and the cleansers and moisturizers that are used. In general, patients with acne should be encouraged to limit washing to twice daily,[11] to use gentle cleansers for sensitive skin, and to avoid scrubs, astringents, or other irritating products. In patients with sensitive skin, a fragrance-free moisturizer, applied over topical medication, may minimize associated irritation. Typically, irritation from the use of topical acne medication peaks at approximately 2 weeks and subsequently abates over time with continued use. Makeup that is labeled "noncomedogenic," "oil-free," or "won't clog pores" can be used to help mask the appearance of the acne until the medications take effect. Patients need to understand that it may take 8 to 12 weeks for clinical

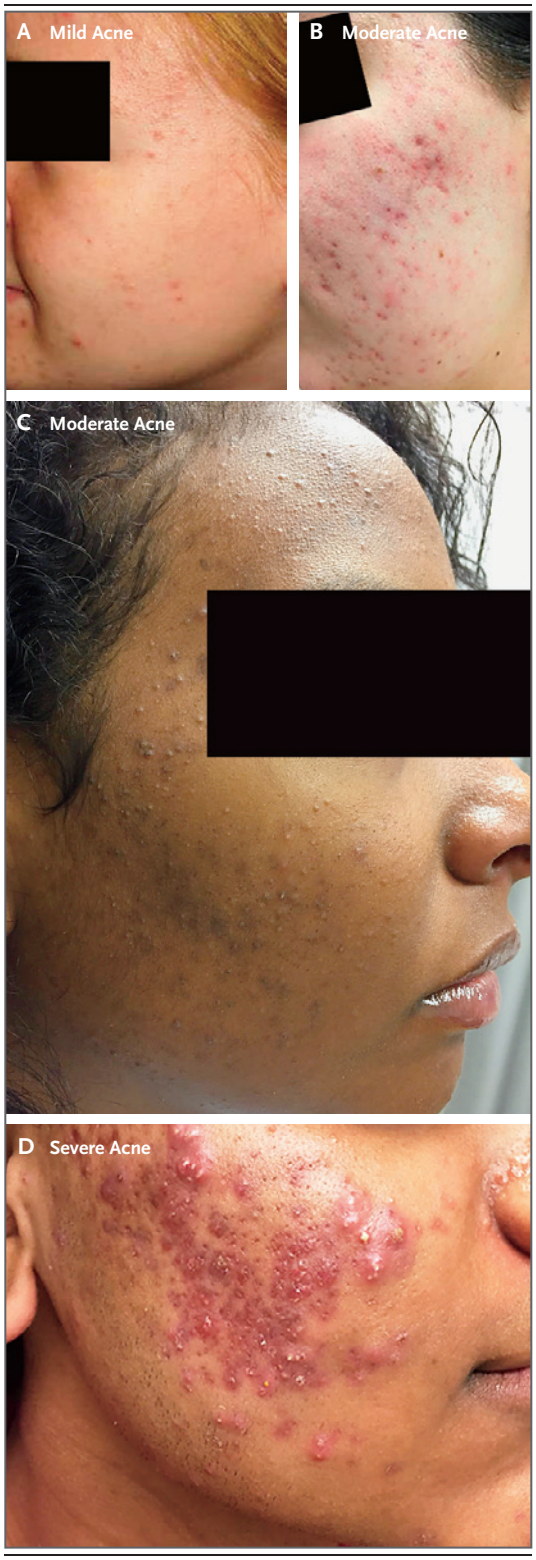

Figure 1. Examples of Acne Severity — Mild, Moderate, and Severe.

Panel A shows a patient with mild acne, with limited papules and pustules and a few closed comedones. Panel B shows a patient with moderate acne, with many papules and notable postinflammatory erythema and pitted scarring. Panel C shows a patient with moderate inflammatory and comedonal acne, with postinflammatory hyperpigmentation noted on the forehead, cheek, and chin. Panel D shows a patient with severe acne, with confluent papules, pustules, and deep nodules.

improvement to occur. Secondary pigmentary changes or erythema typically resolve completely but over a period of many months. The use of sunscreen should be encouraged in patients with postinflammatory hyperpigmentation to prevent further darkening.

Details of an acne treatment algorithm are shown in Table 1. The cornerstone of effective acne management is combination therapy, which targets different pathogenetic mechanisms. Commonly used topical and systemic treatments for acne, including the standard doses, available formulations, and common and notable adverse effects, are listed in Table 2.

Topical Retinoids

A topical retinoid should be used as the foundation for most acne treatment regimens; however, studies show that they are underprescribed by both primary care providers and dermatologists.[14] Topical retinoids are comedolytic, normalize desquamation at the follicular infundibulum, and have antiinflammatory properties. In the United States, three topical retinoids are used in patients with acne: tretinoin, adapalene, and tazarotene. All the retinoids are mildly photosensitizing, but this situation can be managed easily with sunscreen use.

In clinical trials, various tretinoin formulations have resulted in abatement of both comedones and inflammatory lesions, as compared with vehicle. When used as monotherapy, tretinoin 0.025% gel resulted in a reduction in lesion counts of approximately 40% from baseline to day 84.[15] In a follicular biopsy study, tretinoin 0.1% cream resulted in a 50% reduction in microcomedones at 6 weeks and an 80% reduction at 12 weeks.[16] The

Table 1. Algorithm for the Management of Acne Vulgaris.*

Treatment	Mild Acne	Moderate Acne	Severe Acne
First-line treatment	Benzoyl peroxide, topical retinoid, or topical combination therapy	Topical combination therapy; oral antibiotic, topical retinoid, and benzoyl peroxide; oral antibiotic plus topical retinoid; or benzoyl peroxide plus topical antibiotic	Oral antibiotic plus topical combination therapy, or oral isotretinoin
Alternative treatment	Add topical retinoid or benzoyl peroxide (if not using already), or consider alternative retinoid, or consider topical dapsone	Consider alternative combination therapy; or consider change in oral antibiotic; or add combined oral contraceptive, oral spironolactone, or both (in female patients); or consider oral isotretinoin	Consider oral isotretinoin; or consider change in oral antibiotic; or add combined oral contraceptive, oral spironolactone, or both (in female patients)

* Topical combination therapy (benzoyl peroxide and antibiotic agent; retinoid and benzoyl peroxide; or retinoid, benzoyl peroxide, and antibiotic) may be prescribed as a fixed-dose combination product or as separate components. Recommendations for the management of acne were modified from those of Zaenglein et al.[12]

vehicle affects the efficacy, side-effect profile, and compatibility with other topical medications. Standard tretinoin formulations cannot be applied at the same time as benzoyl peroxide and are unstable when exposed to light; microsphere and polyolprepolymer formulations do not have these restrictions.

Comparative trials have shown that adapalene 0.1% gel (now available over the counter in the United States as Differin gel) has efficacy that is similar to that of tretinoin 0.025% gel, with a better safety profile.[17] In a randomized trial, adapalene 0.3% gel had greater efficacy than adapalene 0.1% gel or vehicle (reductions in total acne lesion counts of 45.3%, 41.8%, and 33.7%, respectively).[18] Adapalene is also light-stable and can be used with benzoyl peroxide; fixed-dose combination products (adapalene 0.1% or 0.3% gel with benzoyl peroxide 2.5% gel) are available by prescription. In patients with moderate-to-severe acne, adapalene 0.3% plus benzoyl peroxide 2.5% gel had greater efficacy than adapalene 0.1% plus benzoyl peroxide 2.5% gel or vehicle alone, with a mean percent change from baseline in lesion counts of approximately 68%.[19]

Tazarotene 0.1% gel has been shown to have superior efficacy to adapalene 0.1% gel and tretinoin 0.1% microsponge gel.[20,21] Tazarotene is the only topical retinoid that has been designated as pregnancy category X (indicating that it is a teratogen that should never be used in pregnant or lactating women), on the basis of its dual indication for psoriasis with the potential for use over a greater body-surface area. Therefore, contraceptive counseling is important for all women of childbearing potential who use this medication.

Topical Antimicrobial Agents

In addition to topical retinoids, benzoyl peroxide is a key component of acne therapy. Benzoyl peroxide is highly effective at reducing the concentration of *C. acnes* through the release of free oxygen radicals, without allowing microbial resistance.[22] Higher concentrations (e.g., 10% vs. 5%) may result in increased irritation without substantially greater *C. acnes* killing power or efficacy, depending on the formulation.[23] The combination of a topical retinoid and benzoyl peroxide has greater efficacy than either product alone.[19] Patients ought to be educated regarding the benefit of this over-the-counter product in their combination routine. A survey of patients with acne of all severities for whom benzoyl peroxide was recommended indicated that only approximately 30% of the patients actually obtained this agent, whereas the vast majority obtained recommended prescription acne products.[24]

Topical antibiotic agents, primarily clindamycin and erythromycin, also reduce the concentration of *C. acnes*. Widespread resistance is common; therefore, antibiotics should not be used as monotherapy but rather combined with other agents. Fixed-dose combinations are available, including clindamycin 1% with tretinoin and either clindamycin or erythromycin with benzoyl peroxide. The combination of benzoyl peroxide with a topical antibiotic has been shown to decrease the concentration of antibiotic-resistant strains of *C. acnes* and has greater efficacy than either product alone.[25] However, owing to the excellent bactericidal properties of benzoyl peroxide alone, the complementary comedolytic and antiinflammatory effects of topical retinoids, and efforts to reduce antibiotic

use overall, the use of topical antibiotics in patients with acne is declining.

Other Topical Treatments

Dapsone gel has been shown to have clinical efficacy in patients with inflammatory acne. It has a reasonable side-effect profile and is often used as first-line therapy in patients with sensitive skin, in women with acne, and in women with darker skin tones who have acne.[26-28] Glucose-6-phosphate–dehydrogenase testing is not considered necessary before topical application, even in at-risk populations.[29] However, rare cases of hemolysis, which is worse with the concomitant use of trimethoprim–sulfamethoxazole, have been reported, as has a case of methemoglobinemia that was due to accidental diffuse application in a toddler.[30]

Azelaic acid, a dicarboxylic acid that is used in patients with acne predominantly because of its ability to lighten postinflammatory hyperpigmentation, can also be of benefit in patients with mild inflammatory and comedonal acne. It reverses abnormal keratinization and inhibits the growth of *C. acnes*.

Despite very limited clinical data, salicylic acid, a comedolytic agent available in many different formulations, is widely available in over-the-counter acne treatments. It is considered to be less effective than a topical retinoid but has a reasonable safety profile and is a good initial over-the-counter medication for very mild acne.

Systemic Antibiotics

Oral antibiotics are widely used in patients with acne to gain control of the inflammation in moderate-to-severe acne. Antibiotics should be used in combination with a topical retinoid and benzoyl peroxide. Given concerns regarding increasing antibiotic resistance, current acne treatment guidelines recommend limiting the use of oral antibiotics to 3 to 4 months whenever possible. Clinical improvement should be maintained with the continued use of a topical retinoid, with or without benzoyl peroxide, depending on lesion types. In clinical trials assessing the efficacy of combination therapy, overall lesion counts decreased by approximately 60% at 3 months.[31,32] In a trial of maintenance therapy after a course of antibiotic therapy with adapalene 0.1% gel, 75% of the patients had maintained clinical improvement with adapalene alone, as compared with 54% of those who used placebo gel.[33]

Typically, tetracyclines are prescribed for acne treatment because they decrease the concentration of *C. acnes*, but they also have antiinflammatory effects. They decrease retinoic acid and enzyme degradation, are antiapoptotic and antioxidant, and regulate cell proliferation. In the United States, minocycline is the most commonly used antibiotic for acne, followed closely by doxycycline.[14] Tetracycline is less often used, owing to inconsistent bioavailability and the need for it to be taken on an empty stomach.

Low-dose doxycycline (which is considered to be subantimicrobial and antiinflammatory) has also been studied in an effort to decrease antibiotic resistance and improve the side-effect profile. In patients with moderate-to-severe acne, the use of modified-release doxycycline at a dose of 40 mg daily showed efficacy that was similar to that with doxycycline at a dose of 100 mg daily, and both were superior to placebo.[34] Side effects, particularly gastrointestinal upset, were less common in patients who received 40 mg daily than in those who received 100 mg.

Other antibiotics that are used for the treatment of acne include trimethoprim–sulfamethoxazole, penicillins, cephalosporins, and macrolides. However, data are limited regarding their effects in patients with acne, and their use should be confined to patients who cannot take tetracycline.

Hormonal Therapies

The use of combined oral contraceptive pills — those containing an estrogen and a progestin — has been shown to have effectiveness similar to that of oral antibiotics in controlling inflammatory lesions in adult women with acne, although it takes longer for patients to have clinical improvement. In a meta-analysis of 32 randomized trials, the use of combined oral contraceptives resulted in a 62% reduction from baseline in inflammatory lesions at 6 months.[35] Combined oral contraceptive pills are often used as second-line therapy in adult or adolescent women, including those with PCOS. Currently, Ortho Tri-Cyclen (ethinyl estradiol–norgestimate), Estrostep (ethinyl estradiol–norethindrone), and Yaz or Beyaz (ethinyl estradiol–drospirenone) have been approved by the Food and Drug Administration (FDA) for use in the treatment of acne vulgaris, although most other third- and fourth-generation progestin-containing combined oral contraceptives are also efficacious. First-generation progestins, such as norethindrone

and norgestrel, are androgenic and can therefore exacerbate acne.

The antiandrogen spironolactone is also beneficial in women with acne. Although data from randomized trials of this agent are limited, several retrospective studies and observational data have shown that spironolactone use has been associated with substantial clinical improvement in women with acne.[36-39] Adult women in general and adults and adolescents with PCOS may have a particular benefit. To ameliorate side effects of breast tenderness and menstrual irregularity, spironolactone is often prescribed with a third- or fourth-generation combined oral contraceptive. Spironolactone is contraindicated during pregnancy owing to potential feminization of a male fetus. Hyperkalemia is uncommon, although it is a concern in women who have renal disease or are taking potassium-sparing diuretic agents. Routine monitoring in otherwise healthy women is not recommended.[40]

Table 2. Commonly Used Topical and Systemic Treatments for Acne Vulgaris.

Treatment	Dose and Formulations	Level of Evidence*	Adverse Effects†	Pregnancy Category‡
Topical treatments				
Over-the-counter therapy				
Benzoyl peroxide	2.5–10% wash, bar, gel, foam, lotion or cream daily or twice daily	I and II	Irritation, allergic contact dermatitis, and bleaching of fabrics	C
Adapalene (Differin)	0.1% gel daily	I and II	Irritation and allergic contact dermatitis	C
Salicylic acid	1% wash, gel, pad, and cream daily or twice daily	I	Irritation and allergic contact dermatitis	C
Prescription single-agent therapy				
Erythromycin	2% gel, pad, or solution daily	I and II	Irritation and allergic contact dermatitis	B
Clindamycin	1% pledget, lotion, solution, or foam daily	I and II	Irritation and allergic contact dermatitis	B
Adapalene	0.1% gel or cream daily or 0.3% gel daily	I and II	Irritation and allergic contact dermatitis	C
Tretinoin	0.025%, 0.05%, or 0.1% cream or gel daily or 0.04%, 0.08%, or 0.1% microgel daily	I and II	Irritation and allergic contact dermatitis	C
Tazarotene	0.05% or 0.1% cream, gel, or foam daily	I and II	Irritation and allergic contact dermatitis	X
Dapsone	5% or 7.5% gel daily or twice daily	I and II	Irritation, allergic contact dermatitis, methemoglobinemia,§ and orange staining of skin and hair when used with benzoyl peroxide at same time	C
Azelaic acid		I	Irritation	B
Prescription fixed-dose combination therapy				
Benzoyl peroxide–erythromycin	5% benzoyl peroxide and 3% erythromycin gel daily	I	Irritation, allergic contact dermatitis, and bleaching of fabrics	C
Benzoyl peroxide–clindamycin	5% benzoyl peroxide and 1% clindamycin gel daily; 3.75% benzoyl peroxide and 1.2% clindamycin gel daily; or 2.5% benzoyl peroxide and 1.2% clindamycin gel daily	I	Irritation, allergic contact dermatitis, and bleaching of fabrics	C
Adapalene–benzoyl peroxide	0.1% adapalene and 5% benzoyl peroxide gel daily; or 0.3% adapalene and 5% benzoyl peroxide gel daily	I and II	Irritation, allergic contact dermatitis, and bleaching of fabrics	C
Tretinoin–clindamycin	0.025% tretinoin and 1.2% clindamycin gel daily	I	Irritation and allergic contact dermatitis	C

Table 2. (Continued.)

Treatment	Dose and Formulations	Level of Evidence*	Adverse Effects†	Pregnancy Category‡
Systemic treatments				
Antibiotic agents				
Doxycycline	100 mg daily or twice daily, 20 mg twice daily, or 40 mg daily with modified release	I and II	Gastrointestinal upset, photosensitivity, elevated aminotransferase levels, and pseudotumor cerebri	D
Minocycline	100 mg daily or twice daily	I and II	Gastrointestinal upset, dizziness, blue–gray skin pigmentation, elevated aminotransferase levels, pseudotumor cerebri, autoimmune hepatitis, and serum sickness-like reaction	D
Tetracycline	500 mg daily or twice daily	I and II	Gastrointestinal upset, liver-function abnormalities, and pseudotumor cerebri; agent must be taken on an empty stomach	D
Hormonal agents				
Combined oral contraceptives	Ethinyl estradiol–norgestimate daily, ethinyl estradiol–norethindrone daily, or ethinyl estradiol–drosperinone daily	I	Gastrointestinal upset, headache, mood changes, venous thromboembolism, stroke, and hypertension	X
Spironolactone	25–100 mg daily or twice daily	II and III	Breast tenderness, menstrual irregularity, and hyperkalemia; tumorigenic (in rats)	C¶
Retinoid				
Isotretinoin	0.5 mg/kg/day, increasing to 1 mg/kg/day after 1 mo	I and II	Mucocutaneous dryness, joint pain, decreased visual acuity, night blindness, hyperlipidemia, elevated aminotransferase levels, pancreatitis, pseudotumor cerebri, and mood disturbance	X‖

* Levels of evidence are classified with the use of the Strength of Recommendation Taxonomy as follows: level I (good-quality, patient-oriented evidence [i.e., evidence measuring outcomes that matter to patients, including death, complications, symptom abatement, cost reduction, and quality of life]), level II (limited-quality, patient-oriented evidence), and level III (other evidence, including consensus guidelines, opinion, case studies, and disease-oriented evidence [i.e., evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes]).[13]

† The list of adverse effects is not comprehensive but includes serious adverse effects and common nonserious adverse effects.

‡ Pregnancy categories are classified as follows: category A, controlled studies involving women have not shown a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters) and the possibility of fetal harm appears remote; category B, either reproduction studies in animals have not shown a fetal risk but there are no controlled studies involving pregnant women or reproduction studies in animals have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies involving women in the first trimester (and there is no evidence of a risk in later trimesters); category C, either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and there are no controlled studies involving women or studies involving women and in animals are not available (category C drugs should be given only if the potential benefit justifies the potential risk to the fetus); category D, there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or in the case of a serious disease for which safer drugs cannot be used or are ineffective); and category X, studies in animals or involving humans have shown fetal abnormalities, or there is evidence of fetal risk on the basis of human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit; category X drugs are contraindicated in women who are or may become pregnant. Further details are available at www.perinatology.com/Archive/FDA%20CAT.htm.

§ Methemoglobinemia was reported in a toddler; in typical use in adults, this adverse effect would not be considered to be relevant.

¶ It is recommended that the use of spironolactone be avoided during pregnancy because it may cause feminization of a male fetus.

‖ Isotretinoin is teratogenic and has resulted in cases of the fetal retinoid syndrome.

Isotretinoin

Isotretinoin is a systemic retinoid that is highly effective for treating recalcitrant nodulocystic acne. It is also used in patients with moderate-to-severe acne who do not have a response to other therapy, including oral antibiotics. The specific mechanism of action remains unknown, but it decreases sebum, *C. acnes* concentration, and inflammation

and has strong comedolytic effects. It is a potent teratogen, and various pregnancy-prevention programs are in place worldwide. In the United States, the use of isotretinoin is regulated by the FDA-mandated risk-management program iPLEDGE (further details regarding this program can be found at www.ipledgeprogram.com). Only enrolled providers may prescribe isotretinoin, and they must obtain written informed consent and register every patient (regardless of sex). In patients of childbearing potential, two specific forms of contraception and monthly pregnancy tests are required.

Common cutaneous side effects of isotretinoin include dryness of skin and mucosa. Elevations in serum triglyceride, low-density lipoprotein cholesterol, and aminotransferase levels may occur, although they are usually mild.[41] Routine testing of lipid-panel and liver-function tests are recommended at baseline and once the maximum therapeutic dose is reached.[42] A possible increased risk of inflammatory bowel disease had been reported with isotretinoin use but is not supported by recent data.[43]

One serious concern is a possible link between isotretinoin use and depression and suicide.[44-46] Although prospective studies have shown an overall improvement in depression scores (indicating lessening in depression) in patients with severe acne taking isotretinoin,[47,48] these studies were not powered to detect an increase in the incidence of depression or suicidal ideation. Given that retinoids readily cross the blood–brain barrier and that depression is common in the adolescent population and in patients with severe acne, it is prudent to counsel and monitor patients taking isotretinoin for the risk of depression at each visit.

AREAS OF UNCERTAINTY

A better understanding of the pathogenesis of acne is needed to guide effective, mechanism-targeted treatments. Effects of diet on acne remain uncertain. Diets with a higher glycemic load have been associated with acne in some studies.[49-51] In patients with known insulin resistance, a decreased-glycemic-load diet in conjunction with metformin therapy resulted in decreased acne, as compared with no changes in diet or the use of metformin alone.[50] The effect of a low-glycemic-load diet in patients who do not have insulin resistance is less clear, but small studies have shown reductions in acne lesion counts with a low-glycemic-load diet.[51,52] Several reports have suggested an association between the intake of milk and other dairy products and the presence of acne.[53,54] Further studies are needed before specific recommendations for patients can be endorsed.

Pulsed dye and fractionated CO_2 lasers are occasionally used for the treatment of acne scarring. However, the role of medical devices, including lasers and photodynamic therapy, in the management of acne warrants further study.

GUIDELINES

Guidelines for the management of acne vulgaris in adolescents and adults have been updated by the American Academy of Dermatology, the European Dermatology Forum, and the French Acne Guidelines Working Group[55-57]; all advocate combination therapy and the reduced use of both topical and systemic antibiotics. The recommendations in this article are generally concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The adolescent in the scenario has moderate acne that is resistant to over-the-counter therapy. I would recommend initiating combination therapy with topical adapalene 0.1% gel or tretinoin 0.025% cream nightly, an over-the-counter benzoyl peroxide wash daily in the shower, and doxycycline at a dose of 100 mg daily. If substantial clinical improvement is noted, I would plan to discontinue doxycycline after 3 months and to continue the use of the retinoid and benzoyl peroxide for maintenance therapy. If her acne was not well controlled at follow-up, I would consider alternate therapy, such as a combined oral contraceptive, with or without spironolactone, or perhaps isotretinoin.

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REFERENCES

1. Lynn DD, Umari T, Dunnick CA, Dellavalle RP. The epidemiology of acne vulgaris in late adolescence. Adolesc Health Med Ther 2016;7:13-25.
2. Collier CN, Harper JC, Cafardi JA, et al. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol 2008;58:56-9.
3. Hay RJ, Johns NE, Williams HC, et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. J Invest Dermatol 2014;134:1527-34.
4. Ritvo E, Del Rosso JQ, Stillman MA, La Riche C. Psychosocial judgements and perceptions of adolescents with acne vulgaris: a blinded, controlled comparison of adult and peer evaluations. Biopsychosoc Med 2011;5:11.
5. Mallon E, Newton JN, Klassen A, Stewart-Brown SL, Ryan TJ, Finlay AY. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. Br J Dermatol 1999; 140:672-6.
6. Ramrakha S, Fergusson DM, Horwood LJ, et al. Cumulative mental health consequences of acne: 23-year follow-up in a general population birth cohort study. Br J Dermatol 2016;175:1079-81.
7. Cunliffe WJ. Acne and unemployment. Br J Dermatol 1986;115:386.
8. Bataille V, Lens M, Spector TD. The use of the twin model to investigate the genetics and epigenetics of skin diseases with genomic, transcriptomic and methylation data. J Eur Acad Dermatol Venereol 2012;26:1067-73.
9. Walton S, Wyatt EH, Cunliffe WJ. Genetic control of sebum excretion and acne — a twin study. Br J Dermatol 1988;118: 393-6.
10. Cengiz FP, Cevirgen Cemil B, Emiroglu N, Gulsel Bahali A, Onsun N. Acne located on the trunk, whey protein supplementation: is there any association? Health Promot Perspect 2017;7:106-8.
11. Choi JM, Lew VK, Kimball AB. A single-blinded, randomized, controlled clinical trial evaluating the effect of face washing on acne vulgaris. Pediatr Dermatol 2006;23:421-7.
12. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol 2016;74(5):945-73.e33.
13. Ebell MH, Siwek J, Weiss BD, et al. Simplifying the language of evidence to improve patient care: Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in medical literature. J Fam Pract 2004;53: 111-20.
14. Lee YH, Liu G, Thiboutot DM, Leslie DL, Kirby JS. A retrospective analysis of the duration of oral antibiotic therapy for the treatment of acne among adolescents: investigating practice gaps and potential cost-savings. J Am Acad Dermatol 2014; 71:70-6.
15. Lucky AW, Cullen SI, Jarratt MT, Quigley JW. Comparative efficacy and safety of two 0.025% tretinoin gels: results from a multicenter double-blind, parallel study. J Am Acad Dermatol 1998; 38:S17-S23.
16. Lavker RM, Leyden JJ, Thorne EG. An ultrastructural study of the effects of topical tretinoin on microcomedones. Clin Ther 1992;14:773-80.
17. Grosshans E, Marks R, Mascaro JM, et al. Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life. Br J Dermatol 1998;139:Suppl 52:26-33.
18. Thiboutot D, Pariser DM, Egan N, et al. Adapalene gel 0.3% for the treatment of acne vulgaris: a multicenter, randomized, double-blind, controlled, phase III trial. J Am Acad Dermatol 2006;54:242-50.
19. Stein Gold L, Weiss J, Rueda MJ, Liu H, Tanghetti E. Moderate and severe inflammatory acne vulgaris effectively treated with single-agent therapy by a new fixed-dose combination adapalene 0.3 %/ benzoyl peroxide 2.5 % gel: a randomized, double-blind, parallel-group, controlled study. Am J Clin Dermatol 2016;17: 293-303.
20. Leyden JJ, Tanghetti EA, Miller B, Ung M, Berson D, Lee J. Once-daily tazarotene 0.1 % gel versus once-daily tretinoin 0.1 % microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. Cutis 2002;69:Suppl:12-9.
21. Webster GF, Guenther L, Poulin YP, Solomon BA, Loven K, Lee J. A multicenter, double-blind, randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1% gel and adapalene 0.1% gel for the treatment of facial acne vulgaris. Cutis 2002;69: Suppl:4-11.
22. Leyden JJ, Wortzman M, Baldwin EK. Antibiotic-resistant propionibacterium acnes suppressed by a benzoyl peroxide cleanser 6%. Cutis 2008;82:417-21.
23. Brandstetter AJ, Maibach HI. Topical dose justification: benzoyl peroxide concentrations. J Dermatolog Treat 2013;24: 275-7.
24. Huyler AH, Zaenglein AL. Adherence to over-the-counter benzoyl peroxide in patients with acne. J Am Acad Dermatol 2017;77:763-4.
25. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. J Am Acad Dermatol 1997; 37:590-5.
26. Del Rosso JQ, Kircik L, Gallagher CJ. Comparative efficacy and tolerability of dapsone 5% gel in adult versus adolescent females with acne vulgaris. J Clin Aesthet Dermatol 2015;8:31-7.
27. Alexis AF, Burgess C, Callender VD, et al. The efficacy and safety of topical dapsone gel, 5% for the treatment of acne vulgaris in adult females with skin of color. J Drugs Dermatol 2016;15:197-204.
28. Lynde CW, Andriessen A. Cohort study on the treatment with dapsone 5% gel of mild to moderate inflammatory acne of the face in women. Skinmed 2014; 12:15-21.
29. Piette WW, Taylor S, Pariser D, Jarratt M, Sheth P, Wilson D. Hematologic safety of dapsone gel, 5%, for topical treatment of acne vulgaris. Arch Dermatol 2008;144: 1564-70.
30. Graff DM, Bosse GM, Sullivan J. Case report of methemoglobinemia in a toddler secondary to topical dapsone exposure. Pediatrics 2016;138(2):e20153186.
31. Gold LS, Cruz A, Eichenfield L, et al. Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. Cutis 2010;85:94-104.
32. Zaenglein AL, Shamban A, Webster G, et al. A phase IV, open-label study evaluating the use of triple-combination therapy with minocycline HCl extended-release tablets, a topical antibiotic/retinoid preparation and benzoyl peroxide in patients with moderate to severe acne vulgaris. J Drugs Dermatol 2013;12:619-25.
33. Thiboutot DM, Shalita AR, Yamauchi PS, et al. Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris: a randomized, controlled, investigator-blind follow-up of a recent combination study. Arch Dermatol 2006;142:597-602.
34. Moore A, Ling M, Bucko A, Manna V, Rueda MJ. Efficacy and safety of subantimicrobial dose, modified-release doxycycline 40 mg versus doxycycline 100 mg versus placebo for the treatment of inflammatory lesions in moderate and severe acne: a randomized, double-blinded, controlled study. J Drugs Dermatol 2015; 14:581-6.
35. Koo EB, Petersen TD, Kimball AB. Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne

vulgaris. J Am Acad Dermatol 2014;71:450-9.
36. Charny JW, Choi JK, James WD. Spironolactone for the treatment of acne in women, a retrospective study of 110 patients. Int J Womens Dermatol 2017;3:111-5.
37. Muhlemann MF, Carter GD, Cream JJ, Wise P. Oral spironolactone: an effective treatment for acne vulgaris in women. Br J Dermatol 1986;115:227-32.
38. Isvy-Joubert A, Nguyen JM, Gaultier A, Saint-Jean M, Le Moigne M, Boisrobert E, Khammari A, Dreno B. Adult female acne treated with spironolactone: a retrospective data review of 70 cases. Eur J Dermatol 2017;27:393-8.
39. Grandhi R, Alikhan A. Spironolactone for the treatment of acne: a 4-year retrospective study. Dermatology 2017;233:141-4.
40. Plovanich M, Weng QY, Mostaghimi A. Low usefulness of potassium monitoring among healthy young women taking spironolactone for acne. JAMA Dermatol 2015;151:941-4.
41. Zane LT, Leyden WA, Marqueling AL, Manos MM. A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. Arch Dermatol 2006;142:1016-22.
42. Hansen TJ, Lucking S, Miller JJ, Kirby JS, Thiboutot DM, Zaenglein AL. Standardized laboratory monitoring with use of isotretinoin in acne. J Am Acad Dermatol 2016;75:323-8.
43. Lee SY, Jamal MM, Nguyen ET, Bechtold ML, Nguyen DL. Does exposure to isotretinoin increase the risk for the development of inflammatory bowel disease? a meta-analysis. Eur J Gastroenterol Hepatol 2016;28:210-6.
44. Rademaker M. Adverse effects of isotretinoin: a retrospective review of 1743 patients started on isotretinoin. Australas J Dermatol 2010;51:248-53.
45. Sundström A, Alfredsson L, Sjölin-Forsberg G, Gerdén B, Bergman U, Jokinen J. Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study. BMJ 2010;341:c5812.
46. Halvorsen JA, Stern RS, Dalgard F, Thoresen M, Bjertness E, Lien L. Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: a population-based study. J Invest Dermatol 2011;131:363-70.
47. Marron SE, Tomas-Aragones L, Boira S. Anxiety, depression, quality of life and patient satisfaction in acne patients treated with oral isotretinoin. Acta Derm Venereol 2013;93:701-6.
48. Gnanaraj P, Karthikeyan S, Narasimhan M, Rajagopalan V. Decrease in "Hamilton Rating Scale for Depression" following isotretinoin therapy in acne: an open-label prospective study. Indian J Dermatol 2015;60:461-4.
49. Burris J, Rietkerk W, Shikany JM, Woolf K. Differences in dietary glycemic load and hormones in New York City adults with no and moderate/severe acne. J Acad Nutr Diet 2017;117:1375-83.
50. Fabbrocini G, Izzo R, Faggiano A, et al. Low glycaemic diet and metformin therapy: a new approach in male subjects with acne resistant to common treatments. Clin Exp Dermatol 2016;41:38-42.
51. Kwon HH, Yoon JY, Hong JS, Jung JY, Park MS, Suh DH. Clinical and histological effect of a low glycaemic load diet in treatment of acne vulgaris in Korean patients: a randomized, controlled trial. Acta Derm Venereol 2012;92:241-6.
52. Smith RN, Mann NJ, Braue A, Mäkeläinen H, Varigos GA. A low-glycemic-load diet improves symptoms in acne vulgaris patients: a randomized controlled trial. Am J Clin Nutr 2007;86:107-15.
53. LaRosa CL, Quach KA, Koons K, et al. Consumption of dairy in teenagers with and without acne. J Am Acad Dermatol 2016;75:318-22.
54. Ulvestad M, Bjertness E, Dalgard F, Halvorsen JA. Acne and dairy products in adolescence: results from a Norwegian longitudinal study. J Eur Acad Dermatol Venereol 2017;31:530-5.
55. Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. Pediatrics 2006;118:1188-99.
56. Nast A, Dréno B, Bettoli V, et al. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol 2012;26:Suppl 1:1-29.
57. Le Cleach L, Lebrun-Vignes B, Bachelot A, et al. Guidelines for the management of acne: recommendations from a French multidisciplinary group. Br J Dermatol 2017;177:908-13.