



**SHARON J. LONGSHORE, RPH, MD**

Department of Dermatology, The Cleveland Clinic

**KIMBERLY HOLLANDSWORTH, MD**

University Hospital Dermatology Associates, Inc.,  
Dermatopathology & General Dermatology, University  
Hospitals' Bolwell Health Center, Cleveland

# Acne vulgaris: One treatment does not fit all

## ■ ABSTRACT

With many treatments now available for acne vulgaris, the treatment must be tailored to the type and severity of the lesions. Most mild-to-moderate cases can be treated with a benzoyl peroxide product, a topical or oral antibiotic, a topical retinoid, or a combination of these medications. Antibiotic resistance is becoming a challenge for many once-reliable topical and oral antibiotics.

## ■ KEY POINTS

Medications target the four stages of acne development: sebum production, hyperkeratinization and obstruction of the pilosebaceous follicle, *Propionibacterium acnes* infection, and inflammation.

Topical products have a role for nearly every patient with acne. The selection depends on the acne type, skin type, and severity, and whether the patient is pregnant.

Oral antibiotics are useful in moderate-to-severe acne and are particularly helpful for acne on the chest and back, where topical treatment is less likely to be effective.

One should use bactericidal benzoyl peroxide products in conjunction with antibiotics to reduce antibiotic-resistant bacteria on the skin.

Referral to a dermatologist is recommended for acne that is resistant to conventional treatment, consideration of isotretinoin therapy, intralesional use of triamcinolone acetonide for painful nodules or cysts, and managing scarring.

**W**E NOW HAVE a variety of topical and oral agents to treat acne vulgaris, and the choice of therapy can range from simple and straightforward to intense and complex.

To treat acne effectively, the physician needs to develop a logical and realistic regimen, tailored to the patient's needs, based on the pathophysiology of acne, and taking into account the growing problem of antibiotic resistance. Furthermore, the patient has to be motivated and compliant.

This article discusses how to evaluate acne and devise an appropriate regimen for even difficult cases.

## ■ HOW ACNE DEVELOPS

Acne vulgaris is a disease of the pilosebaceous follicle. It is due to four processes:

**Sebum production**, stimulated by androgens

**Hyperkeratinization**, leading to obstruction of the follicle

**Infection** with *Propionibacterium acnes*, an anaerobic diphtheroid bacterium

**Inflammation** of the follicle and surrounding tissue, caused by enzymes produced by *P acnes*.<sup>4</sup>

## ■ CLINICAL MANIFESTATIONS

Acne typically begins in puberty but may start in adulthood. The primary cutaneous findings are:

- Open comedones (blackheads)
- Closed comedones (whiteheads)
- Papules
- Pustules
- Nodules.

Lesions occur in areas of higher sebum

TABLE 1

### Classification and initial treatment of acne vulgaris

TYPE OF ACNE	BEST TREATMENT OPTIONS
<b>Comedonal</b> (open and closed)	Topical keratolytics Topical retinoids
<b>Inflammatory</b> (papules and pustules)	Topical benzoyl peroxide product Topical or oral antibiotic Topical retinoid
<b>Nodulocystic</b>	Trial of benzoyl peroxide product, oral antibiotic, and topical retinoid Oral isotretinoin

production, including the face, neck, chest, back, and upper arms. Hyperpigmentation frequently follows primary lesions, as can hypertrophic scars, keloids, and pitted scars. Acne caused by exogenous steroids has a unique monomorphic appearance of papules and appears on the upper trunk and upper arms.

**If you suspect androgenism, measure DHEAS, total and free testosterone, and androstenedione**

#### ■ WHY TREAT ACNE?

Acne may cause discomfort, scarring, and psychological distress. For teenagers and adults alike, acne and acne scarring can contribute to low self-esteem, depression, and social phobia.<sup>2</sup> Patients may perceive even clinically mild disease as repulsive to others and may limit their social interactions.<sup>3</sup> With proper treatment, long-term complications, including scarring, can be minimized or avoided.

#### ■ LABORATORY STUDIES

Laboratory studies are generally only performed if acne has been resistant to treatment, hyperandrogenism is suspected, or the patient is taking oral isotretinoin, which requires regular laboratory monitoring.

If hyperandrogenism is suspected, levels of dehydroepiandrosterone sulfate (DHEAS), testosterone (total and free), and androstenedione are measured. An endocrinologist should be consulted if androgen levels are elevated.

#### ■ ONE TREATMENT DOESN'T FIT ALL

It is essential to select a regimen carefully (TABLE 1). Things to consider:

**The type and severity of the acne lesions.** Acne vulgaris can generally be classified into three categories (FIGURE 1):

- Comedonal acne, which responds well to topical keratolytics and topical retinoids
- Inflammatory acne, which usually requires topical and oral therapy
- Nodulocystic acne, which may respond to oral antibiotics but often requires systemic retinoids.

**If hyperandrogenism is present.** Hyperandrogenism should be considered in a female patient with irregular menses, hirsutism, and acne. It is usually caused by adrenal or ovarian dysfunction.

Functional ovarian hyperandrogenism, including polycystic ovary syndrome, is the most common type of gonadal androgen excess.<sup>6</sup> The most severe form is the HAIR-AN syndrome, characterized by hirsutism, androgen excess, insulin resistance, and acanthosis nigricans.

Acne in association with hyperandrogenism is difficult to treat and often requires a multiple drug regimen, including oral contraceptive pills, spironolactone or one of its analogues, and topical agents with or without oral antibiotics.

**The patient's skin type** (ie, dry, oily, or a combination). Oily skin should be treated with gels, which are the most drying. Creams and ointments are the least drying, although alcohol content, which increases dryness, varies. Lotions and solutions generally fall between gels and creams in terms of drying.

**Bacterial resistance.** Propionibacterial resistance to topical clindamycin and erythromycin was reported in 1979,<sup>7</sup> and to oral tetracycline in 1983.<sup>8</sup> In 1996 the prevalence of antibiotic-resistant propionibacteria was estimated at 60%, most often to erythromycin.<sup>9</sup> Resistance to minocycline has been reported as well.<sup>10</sup>

To minimize the development of bacterial resistance, one should:

- Use antibiotics only when necessary
- Encourage strict compliance
- Limit length of therapy



- Avoid unnecessary antibiotic changes in the same patient
- Use bactericidal benzoyl peroxide products in conjunction with antibiotics to reduce antibiotic-resistant bacteria on the skin
- Avoid prescribing antibiotics of different classes for topical and oral therapy.<sup>8</sup>

**Cost and compliance.** It is essential to develop a regimen that fits into the patient's budget and routine. Teenagers are often more likely to comply with quick and easily applied treatments, such as individually packaged pledgets, which can be carried in an athletic bag or backpack.

#### ■ TOPICAL TREATMENTS

Topical products have a role for nearly every patient with acne (TABLE 2). The selection depends on the patient's acne type and skin type, the severity of the acne, and whether the patient is pregnant.

#### **Benzoyl peroxide preparations**

Benzoyl peroxide products have antibacterial and keratolytic properties and are useful for mild-to-moderate acne. Combining benzoyl peroxide with a topical antibiotic (erythromycin or clindamycin) or a topical retinoid is more effective than monotherapy.<sup>11-13</sup>

The most common adverse effects are dryness, erythema, and peeling. In addition, approximately 1% to 3% of people are allergic to benzoyl peroxide.<sup>14</sup> Patients should also be warned that benzoyl peroxide products can bleach clothing and towels.

#### **Salicylic acid products**

Salicylic acid cleansers, creams, and gels have keratolytic, comedolytic, and anti-inflammatory properties. They are a good alternative for those who cannot tolerate benzoyl peroxide washes.

#### **Topical antibiotics**

Topical antibiotics are also used to treat mild-to-moderate acne. They reduce *P acnes* in the pilosebaceous follicle and have some anti-inflammatory effects. Irritation or other side effects to topical antibiotics are rare.

### Types of acne: Comedonal



### Inflammatory



### Nodulocystic



FIGURE 1

TABLE 2

## Commonly prescribed topical treatments for acne vulgaris

BRAND NAME	GENERIC NAME	HOW SUPPLIED	AVERAGE WHOLESALE PRICE
<b>Benzoyl peroxide preparations</b>			
Brevoxyl	Benzoyl peroxide gel 4%	90 g	\$67.71
	Benzoyl peroxide gel 8%	90 g	\$70.42
	Benzoyl peroxide cleansing lotion 4%	297 g	\$48.18
	Benzoyl peroxide cleansing lotion 8%	297 g	\$50.11
	Benzoyl peroxide creamy wash 4%	170 g	\$36.75
	Benzoyl peroxide creamy wash 8%	170 g	\$38.22
Clinac BPO	Benzoyl peroxide 7% gel	90 g	\$40.86
Triaz	Benzoyl peroxide cleanser 3%, 6%, 10%	170 g	\$24.20
	Benzoyl peroxide gel 3%, 6%, 10%	42 g	\$28.68
<b>Salicylic acid preparation</b>			
Neutrogena	Salicylic acid 2% wash	150 mL	\$5.12
<b>Topical antibiotics</b>			
Cleocin T	Clindamycin 1% gel	60 g	\$70.45
	Clindamycin 1% solution	60 mL	\$44.44*
	Clindamycin 1% lotion	60 mL	\$54.42
Clindagel	Clindamycin 1% gel	42 g	\$48.94
Clindets	Clindamycin 1% pledgets	Box of 69	\$65.24
Emgel	Erythromycin 2% gel	27 g	\$30.07 <sup>†</sup>
Klaron	Sodium sulfacetamide 10% lotion	59 mL	\$52.21
<b>Topical retinoids</b>			
Avita	Tretinoin cream 0.025%	45 g	\$68.56
	Tretinoin gel 0.025%	45 g	\$67.07
Differin	Adapalene cream 0.1%	45 g	\$77.56
	Adapalene gel	45 g	\$77.56
	Adapalene pledgets 0.1%	60 count	\$76.68
	Adapalene solution 0.1%	30 mL	\$76.68
Retin-A Micro	Tretinoin 0.1% microsphere gel	45 g	\$75.84
<b>Dicarboxylic acid preparations</b>			
Azelex cream	Azelaic acid 20% cream	30 g	\$48.52
Finevin	Azelaic acid 20% cream	30 g	\$40.44
<b>Combination</b>			
Benzaclin	Clindamycin 1%-benzoyl peroxide 5% gel	25 g	\$57.75

\*Generic available: \$23.00

<sup>†</sup>Generic available: 30 g \$22.24

**Inflammatory  
acne usually  
requires topical  
and oral  
therapy**

**Clindamycin**, a commonly used topical antibiotic, is available as a gel, solution, pledget, and lotion. The lotion may be a good option in women with acne who need a moisturizer.

**Erythromycin** and **sodium sulfacetamide** are also available as topical preparations. *P*

*acnes* is more often resistant to erythromycin than to the other products. The combination of benzoyl peroxide and erythromycin or clindamycin is more effective than either topical antibiotic alone. Combination products are available, or the antibiotic and benzoyl peroxide can be prescribed separately.



Erythromycin topical products are considered the safest topical treatment for acne in pregnant women (category B).

### Topical retinoids

Topical retinoids are the best treatment for open and closed comedones. They are comedolytic, working by normalizing follicular keratinization.

Retinoids are traditionally associated with skin irritation, but new delivery systems make this less of a problem. Retin-A Micro gel releases tretinoin from microspheres, and Avita gel and cream contain a large polymer (polyolprepolymer-2). Adapalene (Differin) gel or cream, which acts on different retinoid receptor subtypes, appears to be the least irritating.<sup>15</sup>

Acne may worsen during the first 3 to 4 weeks of retinoid therapy before improving. Patients with sensitive skin should start by applying the retinoid on alternate nights, and then increase to every night once they can tolerate it.

Patients should be warned about increased photosensitivity and should use sunscreen and sun protection while using these products.

### Dicarboxylic acids

Azelaic acid, a bacteriostatic dicarboxylic acid, helps to normalize keratinization and reduce inflammation. It may cause hypopigmentation, so its use should be monitored in dark-skinned patients.

## ■ SYSTEMIC TREATMENTS

Systemic treatments (TABLE 3) are indicated for moderate-to-severe acne or for mild acne that is resistant to topical regimens. Acne on the back is also best treated systemically.

### Oral antibiotics

Oral antibiotics are useful in moderate-to-severe acne and are particularly helpful for acne on the chest and back, where topical treatment is less likely to be effective. Antibiotics have both antibacterial and anti-inflammatory effects.

**Erythromycin** was one of the most frequently prescribed antibiotics for acne, but

**TABLE 3**

## Systemic acne treatments

### Oral antibiotics

Erythromycin 333–500 mg three or four times a day  
Tetracycline 500 mg twice a day  
Minocycline 50–100 mg daily or twice a day  
Doxycycline 50–100 mg daily or twice a day

### Antiandrogens

Oral contraceptives\*  
Norgestimate/ethinyl estradiol (Ortho Tri-Cyclen)  
Drospirenone/ethinyl estradiol (Yasmin)  
Spironolactone 50 mg daily for 2–4 weeks,  
then 100 mg daily if tolerated

### Retinoid

Isotretinoin 0.5–2 mg/kg/day for 4–6 months  
(most common 1 mg/kg/day)

\*Ortho Tri-Cyclen is FDA-approved for treating acne vulgaris; other low-dose combination oral contraceptives with estrogen dominance are also effective

antibiotic resistance has now become more of a problem.

**Tetracycline** therapy is usually begun at 500 mg twice daily. The dosage may be decreased to once daily after a few months of treatment if the patient is doing well. The drug should be taken on an empty stomach, 1 hour before or 2 hours after a meal. It should not be taken at the same time as calcium and iron supplements, which reduce its absorption.

If a patient's acne is not responding to tetracycline after 8 to 12 weeks of therapy, antibiotic resistance may play a role. Switching the treatment to minocycline should be considered.

**Minocycline** and **doxycycline** tend to be more effective than tetracycline but are more expensive. The dosage is 50 mg to 100 mg once or twice daily. Common adverse effects include nausea, vomiting, and, especially with doxycycline, photosensitivity. Minocycline may rarely be associated with vertigo, blue-black cutaneous pigmentation, autoimmune hepatitis, lupus-like syndrome, pseudotumor cerebri, and pneumonitis.

For patients for whom the traditional antibiotics fail or who cannot tolerate them, other antibiotics may be helpful, including **amoxicillin**, **azithromycin**, **cephalexin**, and

**Acne may worsen during the first weeks of retinoid therapy**

**trimethoprim-sulfamethoxazole.** They should be used only on a limited basis.

### Antiandrogens

Antiandrogens are helpful in female patients with signs and symptoms of androgen excess, such as hirsutism and irregular menses, or if there is an incomplete response to systemic antibiotics.

**Oral contraceptives** suppress gonadotropin release, which in turn inhibits ovarian androgen production. Common side effects include nausea, vomiting, breast tenderness, and irregular bleeding.

*Norgestimate/ethinyl estradiol* (Ortho Tri-Cyclen) was the first low-dose oral contraceptive to be approved by the US Food and Drug Administration for the treatment of acne. In a clinical trial in patients with moderate acne, 93.7% of the treatment group showed improvement, compared with 65.4% in the placebo group.<sup>16</sup>

All low-dose combination oral contraceptives with estrogen dominance are equally effective in the treatment of acne.<sup>17</sup> However, some of the newer progestins may have a more suppressive effect on gonadotropin release, so they are likely to be even more effective.

*Drospirenone/ethinyl estradiol* (Yasmin) is a unique oral contraceptive with both antiandrogenic and antiminerlocorticoid properties. Drospirenone is an analogue of spironolactone and has antiminerlocorticoid activity equivalent to 25 mg of spironolactone.

This drug should be avoided in patients with renal, hepatic, or adrenal problems, which predispose to hyperkalemia. Potassium levels should be checked after the first treatment cycle in patients taking other medications that may also increase potassium.

**Spironolactone** is an androgen receptor blocker that may also be useful in the treatment of acne. It can be started at a dosage of 50 mg once a day for 2 to 4 weeks, and then increased to 100 mg daily if tolerated.<sup>18</sup> Periodic monitoring of potassium levels is suggested. Adverse effects may include headache, irregular bleeding, and breast tenderness.

### Isotretinoin, a systemic retinoid

Isotretinoin (Accutane) is the only medication that acts on all four stages of the patho-

genesis of acne, reducing sebum excretion, follicular keratinization, *P acnes*, and inflammation.

Forty percent to 60% of patients remain clear of acne after a single course of isotretinoin.<sup>20</sup> However, acne may worsen in the first several weeks of therapy before improving.

**Indications.** The decision to use isotretinoin should be made only after consulting a dermatologist. It is approved for the treatment of severe cystic acne, but may also be used for less severe cases under certain circumstances:

- Less than 50% improvement in acne after 6 months of treatment with an aggressive conventional oral antibiotic and topical combination regimen
- Acne that leaves scars
- Acne associated with significant psychological distress
- Acne that significantly relapses during or soon after conventional therapy.<sup>19</sup>

**Adverse effects** include peeling of the lips, headache, myalgias, depression, dry eyes, hyperlipidemia, pancreatitis, agranulocytosis, pseudotumor cerebri, and bone changes.

Isotretinoin is also teratogenic, affecting craniofacial, cardiac, thymic, and central nervous system structures. Patients must use two methods of contraception during therapy. New regulations require two negative pregnancy tests prior to starting isotretinoin, and it is strongly recommended to place adolescents on an oral contraceptive before initiating therapy. Women should also be advised not to try to become pregnant for at least 3 months after completing therapy.

All patients who take isotretinoin should be monitored for signs and symptoms of depression. Although isotretinoin has been reported to cause depression in some patients, there have been no controlled studies that document an increased risk of suicide in patients taking this drug.

All patients should avoid alcohol and use sun protection.

**Laboratory monitoring.** Pregnancy tests should be obtained on a monthly basis for the duration of isotretinoin therapy. Other laboratory tests include:

- Complete blood count with platelets

All low-dose combination OCs with estrogen dominance improve acne



- Liver function tests
- Cholesterol and triglycerides
- Creatinine.<sup>21</sup>

These tests should be followed at monthly intervals for the first 4 months of therapy, then may be discontinued if normal.

**Dosage** is 0.5 to 2 mg/kg/day for 4 to 6 months; most patients receive 1.0 mg/kg/day.

### ■ INTRALESIONAL TREATMENT

#### Intralesional corticosteroids

Intralesional injection of triamcinolone acetonide (Kenalog) reduces the inflammation of erythematous papules and nodules, resulting in pain relief and a decrease in new scarring.

### ■ REFERENCES

1. Krowchuk DP. Treating acne: a practical guide. *Med Clin North Am* 2000; 84(4):811–828.
2. Koo JY, Smith LL. Psychologic aspects of acne. *Pediatr Dermatol* 1991; 8:185–188.
3. Wu SF, Kinder BN, Trunnell TN, Fulton JE. Role of anxiety and anger in acne patients: a relationship with the severity of the disorder. *J Am Acad Dermatol* 1988; 18:325–333.
4. Thiboutot DM. New treatments and therapeutic strategies for acne. *Arch Fam Med* 2000; 9:179–187.
5. Johnson BA, Nunley JR. Topical therapy for acne vulgaris. *Postgrad Med* 2000; 107:69–80.
6. Rosenfield RL, Lucky AW. Acne, hirsutism, and alopecia in adolescent girls. *Endocrinol Metab Clin North Am* 1993; 22(3):507–532.
7. Crawford WW, Crawford IP, Stoughton RB, Cornell RC. Laboratory induction and clinical occurrence of combined clindamycin and erythromycin resistance in *Corynebacterium acnes*. *J Invest Dermatol* 1979; 72:187–190.
8. Leyden JJ, McGinley KJ, Cavalieri S, Webster GF, Mills OH, Kligman AM. *Propionibacterium acnes* resistance to antibiotics in acne patients. *J Am Acad Dermatol* 1983; 8:41–45.
9. Eady EA. Bacterial resistance in acne. *Dermatology* 1998; 196:59–66.
10. Ross JI, Snelling AM, Eady EA, et al. Phenotypic and genotypic characterization of antibiotic-resistant *Propionibacterium acnes* isolated from acne patients attending dermatology clinics in Europe, the U.S.A., Japan and Australia. *Br J Dermatol* 2001; 144:339–346.
11. Eady EA, Bojar RA, Jones CE, Cove JH, Holland KT, Cunliffe WJ. The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant *propionibacteria*. *Br J Dermatol* 1996; 134:107–113.
12. 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; 37:590–595.
13. Berson DS, Shalita AR. The treatment of acne: the role of combination therapies. *J Am Acad Dermatol* 1995; 32:531–541.
14. Sykes NL, Webster GF. Acne: a review of optimum treatment. *Drugs* 1994; 48:59–70.
15. Galvin SA, Gilbert R, Baker M, Guibal F, Tuley MR. Comparative tolerance of adapalene 0.1% gel and six different tretinoin formulations. *Br J Dermatol* 1998; 139:34–40.
16. Lucky AW, Henderson TA, Olson WH, Robisch DM, Lebwohl M, Swinyer LJ. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. *J Am Acad Dermatol* 1997; 37:746–754.
17. Koulianos GT. Treatment of acne with oral contraceptives: criteria for pill selection. *Cutis* 2000; 66:281–286.
18. Shaw JC. Hormonal therapy in dermatology. *Dermatol Clin* 2001; 19:169–178.
19. Thiboutot DM. Acne and rosacea: new and emerging therapies. *Dermatol Clin* 2000; 18:63–71.
20. Odom RB, James WD, Berger TG. Acne. In: Andrews' Diseases of the Skin: Clinical Dermatology, 9th edition. Philadelphia: W.B. Saunders Company; 2000:284–306.
21. Nguyen EH, Wolverson SE. Systemic retinoids. In: Wolverson SE, editor. *Comprehensive Dermatologic Drug Therapy*. Philadelphia: W.B. Saunders Company; 2001:269–310.

It should be performed by a dermatologist.

### ■ WHEN TO REFER

Mild-to-moderate acne can usually be treated by the primary care provider or internist with a combination of a benzoyl peroxide product, a topical or oral antibiotic, and a topical retinoid.

Criteria for referral to a dermatologist are:

- Acne resistant to conventional treatment
- Consideration of isotretinoin therapy
- Consideration of intralesional triamcinolone acetonide for painful nodules or cysts
- Management of acne scarring.<sup>21</sup>

ADDRESS: Sharon J. Longshore, RPH, MD, Department of Dermatology, The Cleveland Clinic, A61, 9500 Euclid Avenue, Cleveland, OH 44195.



**CME**  
**CREDIT**  
**TEST**

Category I CME Credit.  
Test your knowledge  
of clinical topics.

**IN THIS ISSUE**  
**PAGE 735**