



# Overview of the treatment of acne vulgaris

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acnes

Acne vulgaris is one of the most common conditions presented to the family physician. The vast array of topical and systemic medications available can make choosing an appropriate treatment seem overwhelming. Because every case of acne is different, the choice of medication should be selected on a case-by-case basis based on the type of acne, its location and patient factors. In this article, we attempt to provide a concise review of how to quickly diagnose acne based on the type(s) of lesion(s), and how to choose a treatment regimen appropriate for each type. We review the pathophysiology and key clinical features of acne, in addition to treatment options.

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## Epidemiology

Acne is a disorder of the pilosebaceous unit, characterized by skin lesions on the face, chest, and back. In the United States, about 40-50 million people are affected by acne annually. Eighty-five percent of those between the ages of 12 and 24 years have acne. Although it is primarily a disease of adolescence, 12% of women and 3% of men battle it into their fifth decade of life.<sup>1</sup> All races are affected, but Caucasians tend to have more severe forms of acne than African Americans.<sup>2</sup>

## Pathogenesis

The cause of acne is multifactorial, including genetics, hormones, and bacteria. It is known that the number of sebaceous glands that one has is an inherited trait, and that it is unlikely for 1 twin to develop acne of different severity than the other twin.<sup>1</sup> This points to a genetic component. Hormones (such as androgen and testosterone) have a great effect on sebum production by sebaceous glands. Conditions such as polycystic ovarian syndrome, hirsutism, and

high levels of serum testosterone are associated with acne. Many female patients complain of beginning or flaring acne during or shortly before menses. As teenagers are nearing the end of adolescence, many notice a significant reduction in the severity or number of lesions present, likely due to steadying of hormonal levels in the body.

Acne forms in the hair follicles of the skin. Just as cells are shed from the skin's surface, they are shed from within the follicle as well. An increase in this shedding process, along with increased cohesiveness of these cells (retention hyperkeratosis) and increased sebum production leads to the formation of a comedone (obstructed hair follicle containing sebum, keratin, and normal flora). The contents continue to accumulate and inflammation can begin.

A bacterium known as *Propionibacterium acnes* is naturally present deep within the follicle. It is not truly pathogenic, but it contributes to the progression of acne. It accumulates and releases proinflammatory mediators that lead to the formation of papules or pustules, which worsen the severity of the disease. As this occurs, papules or pustules may become nodules or cysts and scarring is a concern.<sup>1</sup>

## Clinical features

Clinical features can vary significantly from mild comedones to fulminant systemic disease. The lesions of acne are

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divided into inflammatory and noninflammatory types. Noninflammatory lesions include comedones. If open to the air, the lipids in the sebum become oxidized and turn black (blackheads or open comedones) (Figure 1). If covered, they are closed comedones (whiteheads). Inflammatory lesions include papules, pustules, and nodules or cysts. Being able to quickly differentiate between the 2 types and identify the type of lesion present is the key to formulating a treatment plan that is appropriate for any given patient (Table 1).

### Differential diagnosis

There are several “mimickers” of acne vulgaris. These include acne rosacea (important differentiation is that there are no comedones present in rosacea), seborrheic dermatitis (positive KOH and flaking at scalp, eyebrows, and hairline), demodex folliculitis, perioral dermatitis (erythema near mouth and unresponsive to acne treatments), and keratosis pilaris (resemble closed comedones on erythematous cheeks, more likely present on upper arms) (Table 2).<sup>2</sup>

### Treatment

There are several factors to consider when choosing medications to treat an individual patient with acne. These include clinical type of acne (inflammatory, comedonal, and pustulocystic), severity (number and size of lesions, and amount of inflammation), oily vs dry skin, menstrual history and signs of hyperandrogenism in women, attempted or failed past treatments, history of acne-promoting medications, and the presence of scarring. Ultimately, the clinical type of acne is most important in determining the appropriate treatment regimen. Goals of treatment include decreasing inflammation and bacterial load (*P. acnes*), and reducing retention hyperkeratosis and sebum production.



**Figure 1** Noninflammatory acne (open comedones or “Black-heads”).

**Table 1** Guide for classifying acne type based on lesion morphology and body region affected

	Noninflammatory acne	Inflammatory acne
Lesion type	Comedones – Open (blackheads) – Closed (whiteheads)	Papules Pustules Nodules Cysts
Most common locations	Central face Less commonly chest and back	Face (any region) Chest Back

### Choosing a treatment-delivery system

The choice of delivery system for topical acne medications depends on the patient's skin type (oily vs dry). Gels may cause some dryness and may be of value for patients with oily skin. Creams and lotions tend to be moisturizing. Solutions are drying but they cover large areas more easily than other preparations (such as acne on the upper back), and, together with foams they are easy to apply to hair-bearing areas.<sup>3</sup>

Mild acne consisting of open and closed comedones with only a few inflammatory lesions is commonly treated with topical agents. These can be used alone or in combination. Topical treatment of acne encompasses 4 main types of medication, each used to attack a different factor implicated in the pathogenesis of the disease: retinoids, antibiotics, benzoyl peroxide, and acids.

### Topical agents

#### Topical retinoids

Retinoids are a class of medications derived from vitamin A, also known as comedolytics. Tretinoin (Atralin and Retin-A)

**Table 2** Differential diagnosis for acne, including key differentiating characteristics

Disorder	Differentiating characteristics
Rosacea	No comedones. Papules on erythematous background
Seborrheic dermatitis	Flaking with occasional papules or pustules at hair lines (eyebrows and scalp), +KOH preparation
Pityrosporum folliculitis	Monotonous-appearing pinpoint papules (face of young female), responsive to topical antifungals
Perioral dermatitis	Red papules around mouth and nares (nonpustular), unresponsive to acne treatment
Keratosis pilaris	Follicle-based, noninflamed, white, pinpoint papules (upper posterior arms and cheeks), seen in atopic individuals more frequently

is the prodrug of this class. Their efficacy lies in their ability to normalize follicular keratinization. They increase follicular cell turnover; causing epithelial cells to shed faster, comedones to be extruded, and the formation of new comedones to be inhibited. In addition, retinoids are known to have some antiinflammatory properties, making them useful for both comedonal and mild to moderate inflammatory acne. They are available in a variety of strengths, and in combination with topical antibiotics such as clindamycin (ZIANA), which increases compliance when both are necessary. An added benefit is that retinoids enhance the penetration of all other topical agents into the pilosebaceous unit. One important clinical feature should be remembered. Benzoyl peroxide inactivates retinoids; therefore, one is applied at bedtime and the other in the morning. Side effects about which patients should be informed include dryness, erythema, and scaling. For this reason, and the fact that it is photolabile, nighttime application is recommended. Application generally begins as every third night and can be advanced to daily, if tolerated, and adjusted for positive results with minimal skin irritation. There is little evidence for systemic absorption of topical retinoids, but as a known teratogen, their use during pregnancy is discouraged. The same is true in women of child-bearing age, unless appropriate contraception is implemented.<sup>4-6</sup>

Adapalene (Differin) is a synthetic retinoid-like compound known to provide benefits slightly less potent than other retinoids, but with less irritation and no photosensitivity. It is available as 0.1% or 0.3% gel, solution, or cream, and may be appropriate for those intolerant of other topicals in this class.

Tazarotene (TAZORAC) is a newer retinoid that tends to be less tolerated as it can be drying, but somewhat more effective at reducing the number of papules and open comedones in mild to moderate acne. Use of a good moisturizer immediately after application will minimize the dryness and irritation that can interfere with patient compliance.<sup>6</sup>

## Topical antibiotics

Topical antibiotics (most commonly clindamycin or erythromycin) are effective in treating mild pustular and inflammatory acne. Antibiotics, although antimicrobial, have inherent antiinflammatory properties. They are frequently used in combination with a retinoid (ZIANA) or benzoyl peroxide (Acanya and BenzaClin). Several trials have demonstrated that topical clindamycin can be as effective as oral antibiotics when used in their typical twice-daily dosing.<sup>7,8</sup> In gel form, clindamycin can be drying, but commonly used clindamycin lotion pads (Cleocin-T Pads) are excellent for patients with dry skin.<sup>6</sup> They are to be applied to clean skin in a very thin layer, leaving no visible residue when dry.

## Benzoyl peroxide

Benzoyl peroxide is comedolytic, antiinflammatory, and bactericidal. Most of its effects are antibacterial, making it

ideal for the treatment of inflammatory acne consisting of papules, pustules, and cysts.<sup>6</sup> It is also beneficial to a lesser degree in comedonal acne because of its keratolytic effects caused by the increasing rate of cell turnover. It reduces the size of sebaceous glands, oxidizes bacterial proteins, and reduces the presence of oil on the skin. Benzoyl peroxide is lipid soluble allowing for much better penetration into the pilosebaceous unit. It causes a drying effect that varies from mild desquamation, to scaliness, to cracking, and should be used every other night at first and titrated to nightly as tolerated. Strengths range from 2.5%, 5%, and 10%. For maximum efficacy, use with clindamycin as a combination topical (Acanya and BenzaClin) is recommended when available. Some athletes and teenagers find bar soap easier to use. Benzoyl peroxide is available in this form as PanOxyl over the counter.

## Acids

Two other topical agents frequently used in the treatment of acne are salicylic acid and azelaic acid (Finacea). Salicylic acid is a keratolytic, bactericidal, and comedolytic agent supplied in concentrations of 3%-6% for use on the face, chest, and back. It acts to decrease cell-to-cell cohesion, allowing for epidermal shedding. It also opens obstructed pores, neutralizes bacteria, and decreases diameter of open pores. It has been used in acne, psoriasis, warts, and other conditions for many years and is the oldest keratolytic agent. Use caution in darker skin types because of increased risk of hyperpigmentation.

Azelaic acid is a dicarboxylic acid found in cereals and animal products. It is thought to normalize keratinization leading to decreased thickness of the stratum corneum. There is some evidence of in vitro activity against *P. acnes* and *Staphylococcus epidermidis*.<sup>9</sup> Azelaic acid is quite useful in patients with very sensitive skin types, who cannot tolerate other topicals. During pregnancy, this is a great substitute to a topical retinoid; though it may not be quite as effective.<sup>10</sup>

## Systemic agents

### Systemic antibiotics

Antibiotics are a mainstay in the treatment of inflammatory acne. They work through several mechanisms to reduce the inflammatory response both directly and indirectly. Most importantly, they reduce the number of bacteria (*P. acnes*) in and around the follicle. They also reduce the inflammatory chemicals produced by white blood cells, and the free fatty acid concentration in the sebum, both of which reduce inflammation.

The prototypical antibiotic used in the treatment of acne is tetracycline. There are 2 other medications in the "tetracycline" class, doxycycline and minocycline. These are discussed later. Tetracycline is typically started at

500 mg twice daily until improvement. It must be taken on an empty stomach and never with calcium-containing foods for maximum absorption and efficacy. Avoid this one in pregnant women and young children, and beware of tooth discoloration and photosensitivity.<sup>11</sup>

Another commonly prescribed antibiotic is minocycline (SOLODYN and Minocin), a tetracycline derivative. It is most useful for pustular acne. It is preferred that this be taken on an empty stomach to aid in absorption. It is usually started at 50-100 mg twice daily. The most common side effect is nausea, but rarely blue skin discoloration can be seen. This medication is less likely to cause photosensitivity than other "tetracycline" antibiotics.<sup>11</sup>

Doxycycline (Doryx and Adoxa) is becoming one of the most popular antibiotics in the treatment of acne. It is typically given as 100 mg twice daily, or in the case of Doryx, 150 mg once daily as a delayed-release tablet (increasing compliance in teens). It is known for significant photosensitivity and should be taken with food because it commonly causes nausea. It is important to keep in mind that like all of the "tetracycline" antibiotics (minocycline and tetracycline) doxycycline is contraindicated in patients less than 9 years of age. It is a great choice for patients with inflammatory, pustulocystic acne.<sup>11</sup>

Erythromycin acts similarly to tetracycline, but should be taken with food because of increased incidence of nausea. It is typically given as 250-500 mg twice daily, and is generally safe to use in pregnancy.<sup>11</sup> Clindamycin is rarely used systemically for acne, but much more commonly, and with fewer side effects, as a topical agent.

A few things to consider when selecting a systemic antibiotic for the treatment of acne include cost, side effect profile, and efficacy. Tetracycline is far and away the least expensive of the above-listed antibiotics, and quite effective. There are however, more side effects associated with its use than others. Manufacturers have responded to patient needs by producing branded minocycline and doxycycline. Doryx is once-daily and comes as a dual-scored tablet of three 50 mg sections.<sup>12</sup> This allows for ease of dose adjustment if necessary. Its delayed release decreases the likelihood of both gastrointestinal upset and photosensitivity. SOLODYN is marketed as a once-daily, weight-based tablet. Minocin is a capsule filled with micropellets that can be poured into applesauce or another food item when the patient cannot swallow a pill. These branded products are however, significantly more expensive than their generic counterparts. Many of the pharmaceutical companies are providing discount cards for these branded antibiotics upon request, bringing their cost to the patient at or below that of a generic like tetracycline or erythromycin. All of these medications can predispose to vaginal yeast infections, but this can be treated as needed. Contrary to popular dogma, the American College of Obstetricians and Gynecologists state that none of these antibiotics has been scientifically shown to decrease the efficacy of oral contraceptives.<sup>13</sup> Therefore, women taking oral contraceptives to prevent pregnancy can be reassured.

## Hormonal agents

Oral contraceptives, in acne treatment, have increased in popularity among patients in recent years possibly due to an increase in their advertisement in media. They are not, however, appropriate for all female patients with acne. The goal in the treatment of acne using hormones is to decrease the effects of androgen produced by the patient. This androgen increases sebum production and can promote the formation of acne lesions. Acne chronologically associated with premenstruation and postmenstruation, is generally the most responsive to hormonal therapy. There are several ways to reduce the production of androgens. They include use of estrogens to directly decrease androgen production, antiandrogens to block androgen receptors, or gonadotropin-releasing hormone agonists to decrease upstream stimulation of androgen production in the hypothalamic-pituitary axis. Hormonal imbalances requiring the use of agents other than estrogens and antiandrogens would be most safely and appropriately managed by a gynecologist or endocrinologist.<sup>10</sup>

Another medication to consider is spironolactone, an antiandrogen. It acts by blocking the androgen receptors on sebaceous glands. Spironolactone is supplied in 25-mg tablets given as 100-200 mg daily. It usually requires several months of use for significant results. This medication was not originally designed for acne, but as a potassium-sparing diuretic. Because of this, it is advisable to monitor the serum potassium level at baseline and every 3-6 months. It has been shown to be very effective in the treatment of premenstrual acne flares. Anecdotally, this medication is also quite effective in treating acne on the jawline in adult females.<sup>10</sup>

## Systemic retinoids

Some acne is resistant to conservative treatments or so severe (either covers extensive surface area or is likely to cause significant scarring) that a systemic retinoid is required. There is really only one medication in this category, isotretinoin (Accutane, Amnesteem, and Claravis). As with topical retinoid medications, this is a vitamin A derivative. It affects all major etiologic factors implicated in the formation of acne lesions. Its actions include dramatic reduction of sebum production (to 10% of pretreatment), follicular keratinization, and ductal and surface *P. acnes* concentration.<sup>14</sup> It is extremely effective, leading to complete remission of acne lesions in 85% of patients within the first 4 months of therapy.<sup>15</sup> Usual dosage is 0.5-1 mg/kg/d for 4-8 months.<sup>16</sup> There are weight-based cumulative dose recommendations, which can be easily referenced, but generally 120 mg/kg is the goal.<sup>16</sup> There are patients who require a repeat course of isotretinoin, but this only occurs in 16% of patients. Many have complete remission indefinitely, or may need antibiotic treatment at some point in the future.<sup>17</sup>

The most common side effects of isotretinoin therapy include cheilitis (23%), dry skin (22%), dry nose or mouth (17%), musculoskeletal complaints (10%), and conjunctivitis (9%).<sup>17</sup> Only a fraction of the patients reporting these side effects require discontinuation of therapy. The use of lip and skin moisturizers is usually sufficient to alleviate symptoms. It is a known teratogen, causing primarily craniofacial, cardiac, and CNS abnormalities. For this reason, women must have monthly urine pregnancy tests and report 2 forms of contraception while on the medication. Liver function studies, triglycerides, and complete blood count must also be obtained prior to starting and after 4-6 weeks on isotretinoin (Table 3).<sup>17</sup>

## Surgical or procedural therapy

### Comedone extraction

At times, it may be necessary to facilitate the healing of comedonal lesions, manually extracting the contents. This is a simple, effective way to reduce the amount of bacteria and pressure in the comedone, thereby reducing inflammation. The process is simple. A comedone extractor is an instrument with a small loop on one or both ends, resembling one curved end of a paper clip. For open comedones (blackheads), the extractor is placed over the comedone with direct

pressure perpendicular to the surface of the skin. For closed comedones (whiteheads), the surface of the comedone is first disrupted, using a small needle or a number 11 scalpel blade. This procedure not only helps reduce the number of lesions faster, it gives the patient a sense of satisfaction that is more immediate than medical therapy alone.

### Intralesional injection

Another in-office procedure is intralesional corticosteroid injection. As can be inferred from the use of steroid here, the target of this adjuvant treatment is inflammatory acne. A syringe is used to inject a small amount of steroid into the acne lesion. There is risk of atrophy to subcutaneous adipose tissue. To avoid this, triamcinolone at a strength of 2.5 mg/mL is injected instead of 40 mg/mL as is used in many other applications. The needle is held 30° off the skin and inserted at the border of erythema of the inflammatory lesion. Injection continues slowly until the lesion blanches. For large lesions, it may be necessary to inject at more than one site to obtain full blanching. Covering the lesion while injecting, after the needle is in place, will prevent steroid and pustule contents from erupting from the pore. This treatment is helpful in inflammatory acne involving large papules and pustules. In general, patient satisfaction is excellent with this treatment. Nearly all inflammation is gone in 18-24 hours.

**Table 3** Advantages, potential side effects, and cost comparison of commonly prescribed systemic acne medications

Systemic medication	Estimated cost per month (\$) (drugstore.com)	Advantage	Potential side effects
Tetracycline—Prodrug (rarely available)	20	Inexpensive	Brown coloration of teeth in prepubescent patients
Doxycycline (generic)	276	Generally covered by insurance without prior authorization	Nausea and photosensitivity
Doxycycline (Doryx)	516	Better compliance (once daily) and less GI upset than generic	Photosensitivity
Minocycline (generic)	240	Generally covered by insurance without prior authorization	Nausea, less photosensitivity than doxycycline, and blue coloration of skin and teeth (uncommon)
Minocycline (Solodyn)	> 800	Better compliance (once daily) and more accurate weight-based tablets	Blue coloration of teeth and skin (uncommon)
Minocycline (Minocin)	600	Capsule can be opened and pellets poured into food for those unable to swallow a tablet	Blue coloration of teeth and skin (uncommon)
Erythromycin	75	Inexpensive and generally safe in pregnancy	Nausea (must take with food)
Amoxicillin	30	Inexpensive and generally safe in pregnancy	Penicillin allergy
Spironolactone	40	Effective for acne in adult women with jawline acne with hyperandrogenic phenotype	Hyperkalemia and dehydration
Isotretinoin (Accutane, Amnesteem, and Claravis)	500-1000	High rate of clearance with one round of treatment and great if scarring or recalcitrant cystic acne	Dry mouth or nose or eyes, hypertriglyceridemia, teratogenic, and transaminitis

GI = gastrointestinal.

## Light therapy

In the 1990s, to augment the classic treatments of acne for resistant lesions, light sources were designed for use in a modality known as photodynamic therapy (PDT). The basic premise of PDT is selective tissue destruction. It involves the application of a photosensitizing agent, an incubation period of minutes to hours, and exposure to a light source that activates the photosensitizer. The most commonly used photosensitizers are a solution of 20% aminolevulinic acid (Levulan Kerastick) or its methyl ester (MAL). These are taken up predominately by highly metabolically active cells like the sebaceous glands of acne lesions, or pre-skin cancers (actinic keratoses). Acne has been shown to be more responsive to photoactivated MAL than aminolevulinic acid, as MAL is preferentially absorbed into the sebaceous unit. When treating acne, the red wavelength of light is more effective. Times for incubation and light exposure vary, but PDT for acne is most effective using red light on MAL that has been under occlusion for 3-4 hours.<sup>18</sup> Most patients claim that the treated area feels like they were slightly sunburned. This modality is advantageous when considering side effects of other treatments for resistant acne, such as isotretinoin. The downside is that the equipment and treatment are costly for the physician and patient, respectively.<sup>18,19</sup>

## Conclusions

There are several things to remember when developing a treatment regimen for an individual acne patient. As in all of medicine, treatment is to be based on appropriate diagnosis. This includes acne type (inflammatory or noninflammatory), lesion type (comedone, papule or pustule, and cyst or nodule), skin type (oily or dry or pigmented), and demographic (child or adult or pregnant or breastfeeding). Based on these factors, an appropriate regimen of medications can be chosen. It is always best to begin therapy with topical agents, if possible. If fulminant, inflammatory disease is present, beginning the patient on systemic antibiotics with a topical retinoid is not unreasonable. These are generalities, as lesion type will always dictate medication choice. Finding

a few medications, with which one is comfortable, from each class to use for each lesion type will simplify the process.

## Disclosures

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Dr Benner has no disclosures to make.

## References

1. Bologna JL, et al: *Dermatology*, 1st ed. New York: Mosby; 2003:531-532
2. Habif TP. *Clinical Dermatology*, 4th ed. Philadelphia: Mosby; 2004:90
3. Abena O. Treatment of acnes vulgaris, Delivery vehicles. Available at: <www.uptodate.com>.
4. Bologna JL, et al: *Dermatology*, 1st ed. New York: Mosby; 2003:539
5. Williams H, Bigby M, Diepgen T. *Evidence Based Dermatology*. London: BMJ Publishing Group; 2003:2003
6. Habif TP. *Clinical Dermatology*, 4th ed. Philadelphia: Mosby; 2004:178-180
7. Mills Jr. OH, et al: Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. *Int J Dermatol*. 1986;25:664
8. Sheehan-Dare RA, et al: A double-blind comparison of topical clindamycin and oral minocycline in the treatment of acne vulgaris. *Acta Derm Venereol*. 1990;70:534
9. Kelly AP. Acne and related disorders. In: Sams WMJ, Lynch PJ, eds. *Principles and Practice of Dermatology*, 2nd ed. New York: Churchill Livingstone; 1996:801-818
10. Freedberg I, et al: *Fitzpatrick's Dermatology in General Medicine*, 5th ed. New York: McGraw-Hill; 1999:2734
11. Freedberg I, et al: *Fitzpatrick's Dermatology in General Medicine*, 5th ed. New York: McGraw-Hill; 1999:777-780
12. Doryx [package insert]: Warner-Chilcott. 2011
13. American College of Obstetricians and Gynecologists. Use of hormonal contraception in women with coexisting medical conditions. *ACOG Practice Bulletin*. 2006;107:1453-1472
14. Bologna JL, et al: *Dermatology*, 1st ed. New York: Mosby; 2003:541
15. Robert S, Stern. A. Uniquely effective drug is teratogenic: the case of isotretinoin. *N Engl J Med*. 1989;320:1007
16. Amichai B, et al: Low-dose isotretinoin in the treatment of acne vulgaris. *J Am Acad Dermatol*. 2006;54(4):644-646
17. Habif TP. *Clinical Dermatology*, 4th ed. Philadelphia: Mosby; 2004:186-189
18. Sakamoto F, et al: Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice. *J Am Acad Dermatol*. 2010; 63(6):183-211
19. <[http://www.medicinenet.com/photodynamic\\_therapy/article.htm](http://www.medicinenet.com/photodynamic_therapy/article.htm)>