Chapter 117: Acne Vulgaris

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 15, Acne Vulgaris.

KEY CONCEPTS

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1. Acne is a highly prevalent disorder affecting adolescents and adults, with a large psychosocial impact.

2. The etiology of this complex disease originates from multiple causative and contributory factors, including genetics and environment. The diagnosis is based on the patient's history and clinical presentation.

3. Acne is a disease of the pilosebaceous unit. Elements of pathogenesis involve defects in epidermal keratinization, androgen secretion, sebaceous function, bacterial growth, inflammation, and immunity.

4. Acne vulgaris is a chronic disorder which cannot be "cured." Goals of treatment and prevention include control and alleviation of symptoms by reducing the number and severity of lesions, slowing progression, limiting disease duration and recurrence, prevention of long-term disfigurement associated with scarring and hyperpigmentation, and avoidance of psychologic suffering. Targeting goals may increase patient adherence to therapy.

5. The most critical target for treatment is the microcomedone. Minimizing or reversing follicular occlusion will arrest the pathogenic acne cascade and involve combining treatment measures to target all pathogenic elements.

6. Nondrug measures are aimed at long-term prevention and treatment. Patients should eliminate aggravating factors, maintain a balanced, low-glycemic load diet, and control stress. Cleanse twice daily with mild soap or soapless cleanser and use only oil-free cosmetics. Comedone extraction in approximately 10% of patients produces immediate cosmetic improvement. Shave infrequently as possible, using a sharp blade or electric razor.

7. First-, second-, and third-line therapies should be appropriate for the severity and staging of the clinical presentation and directed toward control and prevention.

8. Treatment regimens should be tapered over time, adjusting to response. Combine the smallest number of agents at the lowest possible dosages to ensure efficacy, safety, avoidance of resistance, and patient adherence.

9. Once control is achieved, maintenance regimens should be simplified to continue with some suppressive therapy. Therapy must be continued beyond 8 weeks: efficacy is assessed through comedonal and inflammatory lesion count, control or progression of severity, and management of associated anxiety or depression. Safety end points include monitoring for treatment adverse effects.

10. Motivate the patient to continue long-term therapy through empathic and informative counseling.

BEYOND THE BOOK

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Watch the video entitled “Acne” by Dr Sheilagh Maguiness, pediatric dermatologist, available on the Society for Pediatric Dermatology Website (https://tinyurl.com/saa9t4s). This 5-minute video provides a brief overview regarding information patients need to know about acne vulgaris. The video is useful to enhance student understanding regarding what information to provide to patients regarding causes of acne, triggers, cleansing, over-the-counter and prescription options, directions for use, and precautions. It gives a brief summary of take-home points useful to direct counseling.

INTRODUCTION

In this chapter, we review the latest developments in understanding acne vulgaris and its treatment. The contents provide an analysis of the physiology of the pilosebaceous unit; the epidemiology, etiology, and pathophysiology of acne; relevant treatment with nondrug measures; and comparisons of pharmacologic agents, including drugs of choice recommended in best-practice guidelines. Options include a variety of alternatives such as retinoids, antimicrobial agents, hormones, and light therapy. Formulation principles are discussed in relation to drug delivery. Patient assessment, general approaches to individualized therapy plans, and monitoring evaluation strategies are presented.

EPIDEMIOLOGY

1 Acne vulgaris is a chronic disease and the most common one treated by dermatologists. There is a high degree of variability in prevalence, age of onset, distribution, severity, and age of resolution.

The lifetime prevalence of acne approaches 90%, with the highest incidence in adolescents; it affects 9.4% of the general population, with trends reflecting higher rates in urban areas compared to rural villages, although these rates are subject to selection and detection bias due to differential access to providers.[1]

The onset of acne vulgaris during puberty occurs at a younger chronologic age in girls than boys (12% age 25-58 vs 3% in males of the same age) and periodic premenstrual flares may continue until menopause. It is triggered in children by the initiation of androgen production by the adrenal glands and gonads, and it usually subsides after the end of growth. However, to some degree, most patients continue to have symptoms into their mid-twenties, and there is evidence that the duration of acne may last into middle age for most women, recorded in 54% of women and 40% of men older than 25 years of age.[2] In puberty, acne is often more severe in boys in about 15% of cases, which is 10-fold greater than in girls. Women often have more severe forms during adulthood. When untreated, acne usually lasts for several years until it spontaneously remits. After the disease has ended, scars and dyspigmentation are not uncommon permanent negative outcomes.

Genetic factors have been recognized; there is a high concordance among identical twins, and there is also a tendency toward severe acne in patients with a positive family history of acne.

There are believed to be no gender differences in acne prevalence. A systematic review included five studies, with a pooled odds ratio of 1.07 (95% CI 0.42-2.7, males with reference to females), suggesting only a slightly higher odds in males.[3]

An international group of epidemiologists, community medicine specialists, and anthropologists have questioned whether acne might be predominantly a disease of Western civilization.[4] They assert that since acne vulgaris is nearly universal in westernized societies (afflicting 79%-95% of the adolescent population), one causative factor might be the Western glycemic diet. While this hypothesis is based on the observation that primitive societies subsisting on traditional (low glycemic) diets have no acne, the theory awaits validation and acceptance by the dermatologic community.

ETIOLOGY

2 Acne is a multifactorial disease. Genetic, racial, hormonal, dietary, and environmental factors have been implicated in its development. Its psychologic impact can be severe.

Four major etiologic factors are involved in the development of acne: increased sebum production, due to hormonal influences; alteration in the keratinization process and hyperproliferation of ductal epidermis; bacterial colonization of the duct with *Propionibacterium acnes*; and production of inflammation with release of inflammatory mediators in acne sites. These are reviewed in the "Pathophysiology" section later in this chapter.

The role of heredity in acne has not been clearly defined; however, there is a significant tendency toward more serious involvement if one or both parents had severe acne during their youth.

Environmental factors play a major role in determining the severity and extent of acne and may influence the choice of topical treatments. Heat and humidity may induce comedones; pressure or friction caused by protective devices such as helmets, shoulder pads, or pillows, and excessive scrubbing or washing can exacerbate existing acne by causing microcomedones to rupture. Pressure may cause acne lesions to form in patients who do not have acne vulgaris: this variant is called *mechanical acne*. Friction, wool, or other rough textured fabrics and occlusive clothing may also be mechanical irritants. Hair styles that are low on the forehead or neck may cause excessive sweating and occlusion, exacerbating acne. In most cases acne is worse in winter and improves during the summer, suggesting a salutary effect of sunlight. However, in some cases, exposure to sunlight worsens the disease.[5] Studies examining the relationship between tobacco smoking and acne show inconsistent results; however, dermatologists have begun to counsel people to quit tobacco smoking as a potential auxiliary treatment for acne.

The importance of psychologic factors in this prolonged and capricious condition has been repeatedly stressed. Two-thirds of affected teenagers wish that they could speak with their physician and healthcare provider about acne, but only one-third do. Emotions, such as intense anger and stress, can exacerbate acne, causing flares or increasing mechanical manipulation: picking, excoriating, or pinching lesions sometimes subconsciously or in sleep. This is probably the result of increased glucocorticoid secretion by the adrenal glands, which appears to potentiate the effects of androgens.[6]

Dietary influences Current investigations explore associations between dietary influences and acne. Under study are dietary influences as factors in acne development as well as potential treatment modalities. This follows the dismissal of overinterpreted 40-year-old, poorly designed studies that disavowed potential effects of dietary ingestions on acne.[7-9] Three primary influences on development include dairy and growth factors in milk; whey protein in milk; and hyperglycemic-load diets.

A series of studies have linked consumption of dairy products with acne.[10,11] Acne has been positively associated with the reported quantity of milk ingested, particularly skim milk.[12] The Nurses Health Retrospective Study examining diet during high school in 47,355 women found an association between acne and milk intake, suggesting natural hormonal components of milk and/or other bioactive molecules in milk could exacerbate acne.[13]

Lactoferrin is a whey milk protein with anti-inflammatory activity. Lactoferrin-enriched fermented milk ameliorated acne vulgaris, selectively decreasing triacylglycerols in skin surface lipids.[13] Lactoferrin administered as a dietary supplement twice daily in mild-to-moderate acne vulgaris led to an overall improvement in acne lesion counts in adolescents and young adults.[14]

A meta-analysis of observational studies examined association of dairy intake and acne in children, adolescents, and young adults. Any dairy product—including milk, yogurt, and cheese—was associated with an increased odds ratio for acne in individuals aged 7 to 30 years; however, studies were heterogeneous in design, making comparisons difficult.[15]

Other studies suggest a role for insulin-like growth factor (IGF), increased by ingestion of high glycemic loads.[16,17] The strongest evidence supports a high-glycemic-load (HGL) diet as a significant factor in acne. In a randomized controlled trial, patients who eliminated high glycemic index foods showed a significant reduction in acne. Those who consumed a low-glycemic-load diet compared with a conventional HGL diet had improvements of facial acne after 12 weeks. Accompanying changes in physical and endocrinologic parameters suggest that decreases in total energy intake, body weight, and indices of androgenicity and insulin resistance may also be associated with observed improvements in acne.[18] Another study reported an improvement in acne and insulin sensitivity in low-glycemic-load diets compared with controls, suggesting nutrition-related lifestyle factors play a role in acne etiology.[19] Independent effects of weight loss versus dietary intervention need to be isolated. In an Australian study, participants who consumed low-glycemic-load diets had no reported cases of acne.[12]

Other studies showed correlations between increases in the ratio of saturated to monoun-saturated fatty acids, acne lesion counts, and increased sebum outflow, suggesting a possible role of desaturase enzymes in sebaceous lipogenesis and the clinical manifestation of acne. These require further investigation.[20]

Univariate and multivariate analyses were used to examine results of a 2015 French survey of individuals (age 15-24 years) reporting or not reporting acne with associated epidemiologic variables. Daily consumption of chocolate and sweets (odds ratio 2.38) and regular use of cannabis (odds ratio 2.88) was independently and highly associated with acne. Smoking tobacco (>10 cigarettes daily) was highly protective. Respective roles of sugar, lipids, and milk were not investigated.[21]

The role of dietary factors in the development or progression of acne vulgaris cannot be dismissed. The practical recommendations would be to avoid excess sugar and skim milk. Further studies are ongoing, including reviewing antioxidants from nutritional and topical sources and probiotics as potential acne-fighting agents.[12]

PATHOPHYSIOLOGY

3 The pathogenesis of acne includes hyperseborrhea, abnormal follicular keratinization, and *Propionibacterium acnes* proliferation in the pilosebaceous unit. Recent research has shed some new light on the involvement of the sebaceous gland, as well as on the pro-inflammatory activity of the cutaneous microbiome. Acne progresses through the following four major stages:

1. Increased sebum production by the sebaceous gland
2. *P. acnes* follicular colonization (and bacterial lipolysis of sebum triglycerides to free fatty acids)
3. Release of inflammatory mediators
4. Increased follicular keratinization

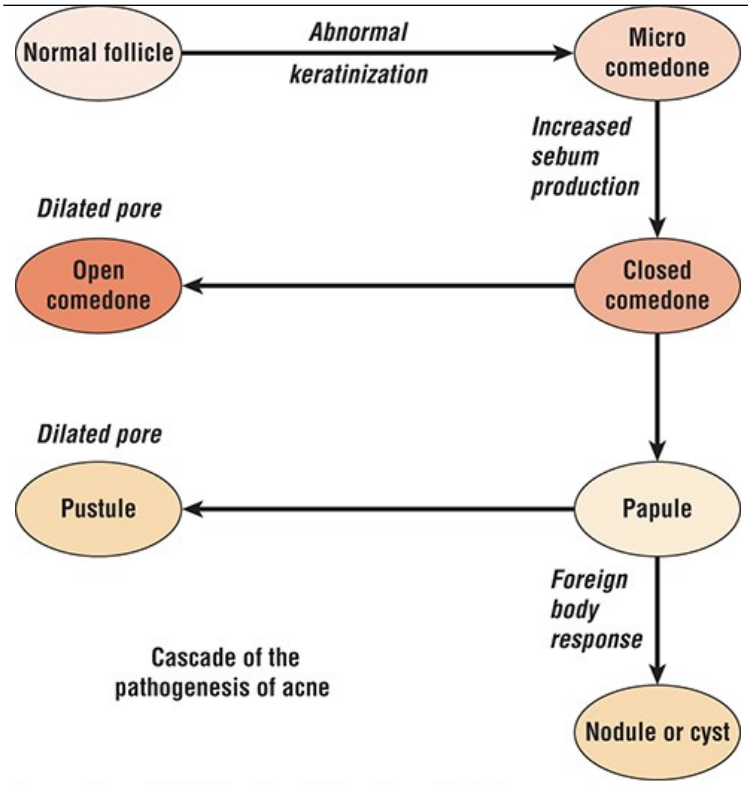
Improved understanding of acne development on a molecular level suggests that acne is a disease that involves both innate and adaptive immune systems and inflammatory events. Receptors that regulate sebaceous lipid metabolism work in concert with receptors regulating epidermal growth and differentiation. Acne can be considered as a model of immune-mediated chronic inflammatory skin disease: an innate immune response that is not able to control *P. acnes* followed by a Th1-mediated adaptive immune response that becomes self-maintaining independently from *P. acnes* itself.[22]

Acne usually begins in the prepubertal period, when the adrenal glands mature, and progresses as androgen production and sebaceous gland activity increase with gonad development. During puberty, alteration of the sebaceous lipid profile, called dysseborrhea, together with stress, irritation, cosmetics, and potential dietary factors lead to inflammation and formation of different types of acne lesions.[23]

As shown in Fig. 117-1, acne results from the development of an obstructed sebaceous follicle, called a *microcomedone*. Sebaceous glands increase their size and activity in response to circulating androgens. Most patients with acne do not overproduce androgens (with some exceptions); instead, they have sebaceous glands that are hyperresponsive to androgens.[24] Patients with acne have a significantly greater number of lobules per gland compared with unaffected individuals.

FIGURE 117-1

Cascade of the pathogenesis of acne. *(Reprinted, with permission, from Mills OH, Kligman AM. Comedogenicity of sunscreens: Experimental observations in rabbits. Arch Dermatol. 1982;18(6):417-419.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Sebum production is induced by different receptors expressed by the sebaceous gland. Involved are the histamine receptor (activated by histamines); the hormonal DHT receptor (activated by androgens); the neuromodulator receptor (mainly substance P); and corticotrophin-releasing hormone (CRH) receptor (mainly activated by stress); molecular research has identified three other receptors that are expressed by the sebocyte and control sebum production. Each of these newly identified receptors is activated by a dietary substance.[23]

The peroxisome proliferator-activated receptors are stimulated by free fatty acids and cholesterol, which act in concert with retinoid X receptors to regulate epidermal growth and differentiation as well as lipid metabolism.

The insulin-like growth factor (IGF)-1 receptor is stimulated by sugar to increase lipid formation, mediated by sterol response element binding proteins. The leptin receptor is stimulated by fat. Leptin is responsible for creating lipid droplets within the sebocyte and induces pro-inflammatory enzyme and cytokine (interleukin [IL]-6 and IL-8) secretion as well.[23]

The sebaceous gland also acts as an endocrine organ in response to changes in androgens and other hormones. Oxidized squalene can stimulate hyperproliferative behavior of keratinocytes, and lipoperoxides produce leukotriene B4, a powerful chemoattractant.[24] The composition of sebum is changed, with a reduction in linoleic acid. The growth of keratinocytes changes. The infrainfundibulum increases its keratinization of cells with hypercornification and development of the microcomedone, the primary lesion of both noninflammatory and inflammatory acne.[22] Cells adhere to each other in an expanding mass, which forms a dense keratinous plug. Androgen hormones could be a stimulus to pilosebaceous duct hypercornification. Sebum, produced in increasing amounts by the active gland, becomes trapped behind the keratin plug and solidifies, contributing to open or closed comedone formation.

Interleukin-1-α upregulation contributes to the development of comedones independently of colonization with *P. acnes.* A relative linoleic acid deficiency has also been described.[24]

A prominent role is played by the follicular colonization by *P. acnes. P. acnes* displays several activities which promote the development of acne lesions, including the promotion of follicular hyperkeratinization; the induction of sebogenesis; and the stimulation of an inflammatory response by the secretion of proinflammatory molecules and by the activation of innate immunity, followed by a *P. acnes*–specific adaptive immune response. In

addition, *P. acnes*–independent inflammation mediated by androgens or by a neurogenic activation, followed by the secretion in the skin of proinflammatory neuropeptides, can occur in acne lesions.[22]

The pooling of sebum in the follicle provides ideal substrate conditions for proliferation of the anaerobic bacterium *P. acnes*, generating a T-cell response, which results in inflammation.[25] *P. acnes* produces a lipase that hydrolyzes sebum triglycerides into free fatty acids. These free fatty acids may trigger the changes that lead to an increase in keratinization and microcomedone formation.[26,27] This closed comedone, or whitehead, is the first clinically visible lesion of acne. It takes approximately 5 months to develop. The closed comedone is almost completely obstructed to drainage and has a tendency to rupture.[28-30]

As the plug extends to the upper canal and dilates its opening, an open comedone, or blackhead, is formed. Its dark color is not due to dirt but to either oxidized lipid and melanin or to the impacted mass of horny cells. The cylindrically shaped, open comedone is very stable and may persist for a long time as soluble substances and liquid sebum escape more easily. Acne that is characterized by open and closed comedones is termed *noninflammatory acne*.

Acne produces chemotactic factors and promotes the synthesis of tumor factor-α and interleukin-1β. Cytokine induction by *P. acnes* occurs. Both recruitment of polymorphs into the follicle during the inflammatory process and release of *P. acnes*–generated chemokines lead to pus formation. The pus eventually bursts on the surface with resolution of the inflammation or into the dermis. *P. acnes* also produces enzymes that increase the permeability of the follicular wall, causing it to rupture, releasing keratin, hair, and lipids and irritating free fatty acids into the dermis. Several different types of inflammatory lesions may form, including pustules, nodules, and cysts and may lead to scarring.

Postinflammatory hyperpigmentation (PIH) and scarring are two sequelae of acne. A time delay of up to 3 years between acne onset and adequate treatment correlates to degree of scarring and emphasizes the need for early therapy.[7,8]

CLINICAL PRESENTATION

To correctly diagnose acne vulgaris, the clinician considers patient assessment, which includes distinguishing all the presenting signs and symptoms of the clinical presentation, reviewing diagnostic and assessment considerations (see Clinical Presentation box), as well as considering psychosocial issues, differential diagnosis, and the possibility of drug-induced acne.

CLINICAL PRESENTATION: Acne Vulgaris

Lesion Type: Acne Vulgaris Can Be Noninflammatory or Inflammatory

- Noninflammatory acne is characterized by open and closed comedones that develop from the subclinical microcomedo
- The closed comedo is visible as a 1 to 2 mm whitehead most easily seen when the skin is stretched. It is often inconspicuous with no visible follicular opening
    - Is the first clinical sign of acne
    - Has a tendency to rupture
- The open comedo or blackhead is large, approximately 2 to 5 mm, and dark-topped with contents extruding
    - is relatively stable
- Inflammatory acne is traditionally characterized as having papulopustular and/or nodular lesions, which may arise from the microcomedo or from noninflammatory clinically apparent lesions
- A pustule is formed from a superficial aggregation of neutrophils
    - Appears as a raised white lesion filled with pus, usually less than 5 mm in diameter

- Superficial pustules usually resolve within a few days without scarring

- A nodule is produced through deeper, dermal, inflammatory infiltration
  - Is the most severe variant of acne
  - Appears as warm, tender, firm lesions, with a diameter of 5 mm or greater
  - May be suppurative or hemorrhagic within the dermis, may involve adjacent follicles and sometimes extend down to fat
- Cysts are suppurative nodules named because they resemble inflamed epidermal cysts
  - Cystic acne may show double comedones, resulting from prior inflammation and fistulous links between neighboring sebaceous units
- Progression of inflammatory lesions
  - Pustules and cysts often rupture spontaneously and drain a purulent or bloody but odorless discharge[31]
  - Inflammatory lesions may itch as they erupt and can be tender or painful. Nodules may develop exudative sinus tracts resulting in tissue destruction
  - Often resolution of these lesions leaves erythematous or pigmented macules that can persist for months or longer, especially in dark-skinned individuals
- Nodules and deep lesions may result in scarring

Regions of Involvement

- Acne lesions can occur anywhere on the body apart from the palms and soles
  - Are usually located on the face, back, neck, shoulders, and chest
  - May extend to buttocks or extremities
  - One or more anatomic areas may be involved in any given patient
  - The pattern of involvement, once present, tends to remain constant
  - Comedones frequently have a midfacial distribution in childhood and, when evident early, are indicative of a poor prognosis
  - Skin, scalp, and hair are frequently oily

Severity Grading Taxonomies

US Food and Drug Administration (FDA) Investigator Global Assessment 2005[31]

Type 1	Almost clear: rare noninflammatory lesions with no more than 1 small IL
Type 2	Mild, some noninflammatory lesions, no more than a few inflammatory lesions (papules/pustules only, no nodules)
Type 3	Moderate: many noninflammatory lesions, some inflammatory lesions, no more than one nodule
Type 4	Severe: up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions

European Union Guidelines Clinical Classification[32,33]

I	Comedonal acne
II	Mild-to-moderate papulopustular (MMPP) acne
III	Severe papulopustular acne, moderate nodular acne (*this level combines FDA types 3 and 4, above*)
IV	Severe nodular acne, conglobate acne (*this is an additional level beyond the FDA types above*)

Diagnostic and Assessment Considerations

Palliating factors	Sunlight
Provoking factors	Premenstrual flares, humid environments, excessive sweating; exposure to chemicals; occlusive clothing; friction; oily cosmetics; manual manipulation; stress; diet (high glycemic load, dairy)
Associated symptoms	Itch, pain, fever
Medical conditions	May contribute to or coexist with acne, including endocrine factors (eg, irregular menses, hirsutism, alopecia), pregnancy, atopy
Allergies	May cause acne symptoms, or present a contraindication to therapy
Medication history	Products may cause or interact with acne signs and symptoms
Social habits	Diet or smoking
Family history	Genetic predisposition to acne
Psychosocial issues	Assess global and disease-specific quality of life (QOL) indicators or health-state utilities

Psychosocial Issues

Acne causes profound negative psychological and social effects on the quality of life (QOL) of patients. Assessment of acne's impact on QOL is an important consideration in clinical decision-making. The negative impact of facial acne is one of the primary motivators for patients to seek and to adhere to treatment.[34] The European Dermatology Forum S3-Guideline for the Treatment of Acne recommended adopting a QOL measure as an integral part of acne management.[35] Specific QOL indicators represent patients' perceptions of and reactions to their health. Assessing QOL impairment in patients with acne may aid in management by evaluating psychologic impact, which may not correlate with clinical severity; aid in detection of depression or need for psychologic care; and improve therapeutic outcomes.

Acne adversely affects all aspects of QOL. In addition to documentation regarding acne-specific QOL impairment, acne impact on general health and

psychologic status has been assessed for relationship between sociodemographic variables, disease severity, and mental status on QOL of acne sufferers. In a report of 195 cases, acne impact on health status was worse compared to other chronic diseases. Authors concluded acne is not a minor disease in comparison with other chronic conditions. Age of onset is capable to influence general health quality (GHQ status), which in turn affects QOL.[36] Patients with acne experience functioning and emotional effects from their skin disease comparable with those experienced by patients with psoriasis, and patients with severe acne reported levels of social, psychological, and emotional problems as great as those reported by patients with chronic disabling asthma, epilepsy, diabetes, back pain, or arthritis.[35]

The European Academy of Dermatology and Venereology Task Force on QOL and Patient Oriented Outcomes and the Task Force on Acne, Rosacea and Hidradenitis Suppurativa have documented the QOL instruments that have been used in acne patients, with information on validation, purposes of their usage, description of common limitations and mistakes in their usage, and overall recommendations.[35]

There are many global scales that have been used to evaluate acne. Some include the World Health Organization Quality of Life (WHOQOL), Skindex,[37] the Dermatology QOL Index,[38] and the Children's Dermatology Life Quality Index (CDLQI). Examples of acne-specific scales include the Acne-specific QOL questionnaire,[39] the Acne QOL Scale,[40] the Acne Disability Index (ADI), and the Cardiff Acne Disability Index (CADI).[35] The Acne QOL Scale was developed to measure the impact of facial acne across four domains (acne symptoms, role-emotional, self-perception, and role-social) of health-related QOL. Health-state utilities (such as time trade-off [TTO]) are quantitative measures of patient preferences of health outcomes ranging from 0 (death) to 1 (perfect health) and can be used in clinical trials as outcome measures of treatment effects. TTO utilities for acne in the range of 0.94 to 0.96 can be compared with those of other diseases (eg, 0.92 for epilepsy, 0.94 for myopia), and help to identify the impact of acne on self-perception and psychologic functioning.[41]

Differential Diagnosis

Acne vulgaris is rarely misdiagnosed. The conditions most commonly mistaken for acne vulgaris include rosacea, perioral dermatitis, gram-negative folliculitis, and drug-induced acne.[42]

Acne rosacea (adult acne) is a chronic, progressive relapsing condition occurring after age of 30 years in fair-complexioned persons. The diagnosis is clinical and based on history and physical findings. There are four subtypes: erythematotelangiectatic changes (erythema, flushing, telangiectasia [spider veins], stinging and burning); progressing to papular-pustular changes (inflammatory lesions, with edema, papules, and pustules on central facial areas such as nose, cheeks, chin, and forehead); phymatous changes (thickened skin and prominent pores on nose, ears, chin, and eyelids); and ocular changes (foreign body sensation, dryness, burning, eyelid erythema).

Rosacea has key differences from acne vulgaris. Onset is not linked to androgens or endocrine changes; and comedones are not usually present. Aggravating factors include endogenous triggers: ingestion of alcohol, spicy foods, or hot drinks (especially those containing caffeine), smoking; and exogenous triggers: overexposure to sunlight; exposure to temperature extremes, heat and humidity, friction, irritating cosmetics, and steroids. Treatment may include antibiotics, particularly doxycycline (low, anti-inflammatory dose) or erythromycin, topical metronidazole, pimecrolimus or azelaic acid as well as agents to reduce erythema (alpha adrenergics).[43]

Perioral dermatitis occurs primarily in young women and adolescents and is characterized by erythema, scaling, and papulopustular lesions commonly clustered around the nasolabial folds, mouth, and chin. The cause is unknown.[44]

Gram-negative folliculitis (*Proteus, Pseudomonas, Klebsiella*) may complicate acne, with a sudden change to pustules or large inflammatory cysts occurring after long-term treatment of acne with oral antibiotics. Folliculitis may be caused by staphylococci. There is a sudden onset of superficial pustules around the nose, chin, and cheeks. Patients with suspected folliculitis should be referred.[45]

Several conditions include acne vulgaris as a characteristic component, and understanding the mechanisms involved in these syndromes provides insight into the pathogenesis of acne. These include polycystic ovary syndrome (elevated androgen levels); PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, acne; early onset arthritis with increased inflammatory activity), and SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis syndrome; sterile inflammatory arthro-osteitis, with *P. acnes* as a possible trigger).[25]

Drug-Induced Acne

In addition to the conditions induced by drugs that are presented in Chapter e121, "Drug-Induced Dermatologic Disorders," acneiform eruptions can also be caused by medications. Drug-induced acne is monomorphic, either comedonal with some inflammation or papular–pustular. Drugs most commonly implicated in inducing comedonal/inflammatory acne include those with hormonal effects (steroids, OCP), halogens (iodide, bromide), vitamins (B_2, B_6, B_{12}), tuberculostatic drugs (isoniazid, ethambutol), lithium salts, antiepileptics (phenytoin), cyclosporine, and azathioprine. Drugs that most commonly induce papular–pustular reactions include anti-inflammatory medications (NSAIDs), sulfamethoxazole–trimethoprim, cephalosporins, and diltiazem.

Systemic corticosteroids can cause a pustular inflammatory form of acne, especially on the trunk. Onset is abrupt at 2 to 6 weeks after initiation of therapy. Acne has also been associated with most of the potent topical steroids, but not with hydrocortisone, which lacks the ability to inhibit protein synthesis. Discontinuation of the steroid results in an initial worsening of appearance due to removal of the anti-inflammatory action of the steroid itself. Caution patients about this reaction, which can be subdued through judicious use of topical hydrocortisone.[44-47]

Antiepileptics and tuberculostatics are the most commonly implicated in drug-induced acne, followed by lithium. Other heavy metals inducing acne include cobalt (in vitamin B_{12}).[48] Halogens, especially an excess of iodide in seafood, salt, and health foods, can exacerbate acne. In addition, halogens can provoke de novo acne lesions in individuals who have increased external exposure often due to occupational contact, or pool or hot tub disinfection; this variant is called *chloracne*.

In addition, certain minor ingredients in cosmetics have been implicated in cosmetic acne, including isopropyl myristate, cocoa butter, and fatty acids.

TREATMENT

The first step in determining a safe and efficacious treatment regimen for acne vulgaris is to establish desired outcomes for the patient, regarding both short- and long-term goals.

Desired Outcomes (Goals of Treatment)

4 Acne vulgaris is treated as a chronic disease, as it demonstrates typical chronicity characteristics: manifests as either acute outbreaks or slow onset; patterns of recurrence or relapse; a prolonged course; and psychologic and social impact. There are two governing principles: the chronic nature warrants early and aggressive treatment, and maintenance therapy is often needed for optimal outcomes.

Acne requires long-term control. This must be stressed with the patient to encourage adherence to lengthy treatment regimens, which address management of current symptoms and signs and preventive measures.

Basic goals of treatment include alleviation of symptoms by reducing the number and severity of lesions (objective and subjective grading) and improving appearance, slowing progression, limiting duration and recurrence, prevention of long-term disfigurement associated with scarring and hyperpigmentation, and avoidance of psychologic suffering.

A significant percentage change in lesion counts is desirable: most patients empirically validate a margin of 10% to 15% reduction in facial lesion counts as appropriate. Patient global self-assessment of acne improvement is a primary outcome.

General Approach to Treatment

5 The most critical treatment target is the microcomedone. Eliminating follicular occlusion will arrest the whole acne cascade. Nondrug and pharmacologic treatment and preventive measures should be directed toward cleansing, reducing triggers, and combination therapy targeting all four pathogenic mechanisms. Combination therapy is often more effective than single therapy and may decrease side effects and minimize resistance or tolerance to individual treatments.

The approach to acne management is largely determined by:

1. Severity index

2. Lesion type: predominantly noninflammatory or inflammatory
3. Treatment preferences including patient choices
4. Cost implications
5. Skin type and/or ethnic group
6. Patient age
7. Adherence
8. Response to previous therapy
9. Presence of scarring
10. Psychologic effects
11. Family history of persistent acne

Topical therapy is the standard of care for mild-to-moderate acne. Those with moderate-to-severe acne will require systemic therapy.

Topical treatments work only where applied. To reduce new lesion development, they must be applied to the entire affected area rather than individual spots. Most cause initial skin irritation, which may result in nonadherence or discontinuation. Irritation can be minimized by starting with lower strengths and gradually increasing frequency or dose. Where irritation persists, changing formulation from alcoholic solutions to washes, gels, or more moisturizing creams or lotions might help.

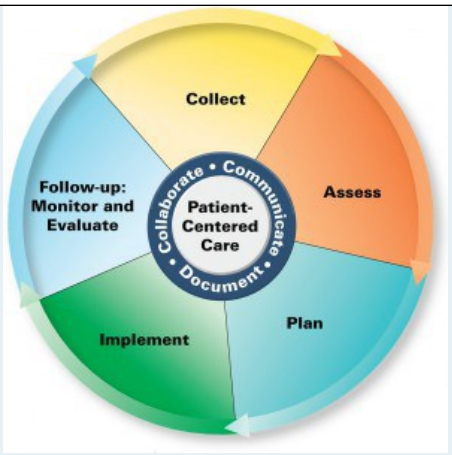
[6] [7] First-line, second-line, and third-line therapies should be selected and altered as appropriate for the severity and staging of the clinical presentation. Treatment is directed at control, not cure. Regimens should be tapered over time, adjusting to response. Combine the smallest number of agents at the lowest possible dosages to ensure efficacy, safety, avoidance of resistance, and patient adherence. Once control is achieved, simplify the regimen but continue with some suppressive therapy. As it takes 8 weeks for a microcomedone to mature, therapy must be continued beyond this duration to assess efficacy. With the exception of topical antibiotics, most topical preparations may be used for years as needed.

Lesions typically recur for years. Microcomedones significantly decrease during therapy but rebound almost immediately after therapy is discontinued. The strategy for treating acne includes an induction phase followed by a maintenance phase, further supported by adjunctive treatments and/or cosmetic routines. Routine maintenance therapy involves regular use of appropriate agents to ensure remission and reduce potential for recurrence of visible lesions.

For successful long-term treatment, maintenance therapy must be tolerable, appropriate for the patient's lifestyle and convenience, continuing months to years, depending on age. Education about pathophysiology of acne and the psychosocial benefits of clearer skin are compelling reasons for patient adherence to consistent therapy to sustain remission.

PATIENT CARE PROCESS

Patient Care Process for Acne Vulgaris



Collect

- Patient characteristics (eg, age, race, sex, weight [body mass index], pregnant)
- Patient medical history (personal and family history, especially of acne or scarring, adrenal abnormalities)
- Social history (eg, psychosocial issues) and dietary habits including intake of glycemic foods, dairy, and sugary drinks (see Clinical Presentation/Diagnostic and Assessment Considerations; also section "Etiology")
- Current medications including OTC drug and nondrug measures, prescription drugs (eg, contraceptives) sunscreens, herbal products, dietary supplements, and prior acne medication use
- Current cosmetic use, including makeup, coverups, and cleansers
- Current use of devices (eg, comedone extractors)
- Inhaled systemic or contact allergies to drugs, cosmetics, foods, vehicle ingredients or excipients
- Objective data
    - Fitzpatrick phototype
    - Labs if relevant to monitoring for hepatic or renal function

Assess

- Presence of provoking factors or contributing factors (see Clinical Presentation/Diagnostic and Assessment Considerations) (eg, hormonal or adrenal anomalies: presence of vellus hair on females; in children: early age of onset [age 1-7 years], body odor, hair in axillary and pubic areas; and adrenal: rapid growth in children)
- Severity: number, type, and region of lesions; presence of scarring
- Hyperpigmentation of healed lesions (postinflammatory hyperpigmentation)
- Ability/willingness to adhere to long-term therapy
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Goals: clear existing and prevent new lesions; reduce scarring, hyperpigmentation, and psychological impact

- Discontinuation of provoking habits, botanicals, or drug or nondrug measures
- Cleansing routine
- Drug therapy regimen including dietary, nonpharmacologic, and pharmacologic approaches
- Monitoring parameters including efficacy (eg, improvement or resolution of lesions and time frame) and safety (eg, sign and symptoms worsening, irritation, or allergy); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug-specific information, medication administration, or application technique)
- Self-monitoring for resolution of acne symptoms, occurrence of scarring, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, behavioral health, dietitian)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, adherence assessment

Follow-up: Monitor and Evaluate

- Improvement or resolution of acne symptoms (eg, noninflammatory or inflammatory lesions)
- Prevention of complications (eg, scarring, infection)
- Slow progression
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate duration of therapy every 3 months

****Collaborate with patient, caregivers, and other healthcare professionals.***

Nonpharmacologic Therapy

8 9 Encourage patients with acne to discontinue or avoid aggravating factors, including occlusion from mechanical factors or cosmetics, maintain a balanced, low-glycemic-load diet, and control stress. By being empathic and informative during counseling, the health professional may motivate the patient to continue long-term therapy.[1,4,43] One of the first approaches to nondrug management of acne is attention to cleansing techniques. Shaving recommendations, comedone extraction, dietary considerations, issues relating to ultraviolet light, and prevention of cosmetic acne should be reviewed with patients.

Cleansing

A systematic review of clinical evidence for washing and cleansers reported that they are common interventions. Cleansers are indicated in all patients with acne. However, the clinical evidence for their efficacy is not well understood.[49]

Twice-daily face washing may be superior to either once-daily or more frequent washing. Washing too frequently in an attempt to remove surface oils has no added benefit and is not likely helpful, as surface lipids do not affect acne. Contributory lipids are deep in the follicle and are not removed

through washing. Antiseptic cleansers, while producing a clean, refreshed feeling, remove only surface dirt, oil, and aerobic bacteria. They do not affect *P. acnes.* Patients should wash no more than twice daily with a mild, nonfragranced opaque or glycerin soap or a soapless cleanser.

Bar soaps are subclassified into true soaps, comprising an alkali and a fatty acid, syndet bars, which use synthetic surfactants, and combars, which include features of both. A study has suggested syndet bars may be superior to true soaps as an acne vulgaris cleansing agent.[50]

Soapless cleansers are an alternative to soaps.[51] Soaps are the most widely used cleansing products, but do not lend themselves to efficient delivery of active drug. Two main disadvantages exist. As soaps are rinsed off, the deposit of active agent is limited, and the high pH required in soaps may degrade some active ingredients and be less tolerable on sensitive skin. Soaps produce a drying effect on the skin due to detergent action. As medicated cleansers require increased contact time, this drying action is pronounced, especially with peeling agents.

Gentle liquid cleansers often contain surfactant systems to remove dirt, sebum, bacteria, and corneocytes from the skin surface. Oil is dispersed from the skin into the surfactant system; however, the active ingredient is sometimes trapped and removed upon rinsing. The balance between cleanliness and drying or irritation should also be considered. Most patients prefer products with foaming action, and these must contain additional secondary surfactants to enhance the foam and condition the skin.

There is no evidence that any particular washing regimen is superior. Evidence-based studies on the use of cleanser or medicated cleansers are lacking or poorly designed with small numbers of patients.[52] It is also difficult to compare studies of different nonprescription formulations even when the same active ingredient is used, as differences in the composition of vehicle may affect cutaneous penetration and vehicles themselves may affect acne. Avoid cream-based cleansers. Scrubbing should be minimized to prevent follicular rupture.

Because the acid pH of skin has an antimicrobial effect, it has been proposed that lowering lesional surface pH (with products such as Herpifix, marketed in Europe) may be correlated to the number of acne lesions. Studies are planned.

Synthetic polyester cleansing sponges abrade the skin surface, removing superficial debris. Considering the structure of comedones, they are unlikely to unseat these lesions. Sponges are available in soft or coarse textures, with or without soap. Circular or rubbing motions will increase irritation. Instruct patients to use single, gentle, continuous strokes on each side of the face, from the midline out toward the ears.

Cationic-bond strips are activated by water. As the strip dries, the cation bonds with the anionic dirt and oil in the pores and removes it when the strip is peeled off.

Shaving

Boys and men with acne should try electric and safety razors to determine which is more comfortable for shaving. When using a safety razor, the beard should be softened with soap and warm water or shaving gel. Shaving should be done as lightly and infrequently as possible, using a sharp blade and being careful to avoid nicking lesions. Strokes should be in the direction of hair growth, shaving each area only once, to minimize irritation.

Comedone Extraction

Comedone extraction has not been widely tested in clinical trials despite long-standing clinical use; however, it is painless and results in immediate cosmetic improvement. Pretreatment with a peeler for 4 to 6 weeks often facilitates the procedure.[47] Following cleansing with hot water, a comedone extractor is placed over the lesion and gentle pressure applied until the contents are expressed. This removes unsightly lesions, preventing progression to inflammation. A correctly sized extractor allows the central keratin plug to extrude through the opening. The small end of a plastic eye dropper, with bulb removed, may also be used. These instruments should be cleaned with alcohol after each use. Some initial reddening may be apparent. If the contents are not expressed with modest pressure, patients should not continue since improper extraction may further irritate the skin. A physician should be consulted if this technique is too difficult for the patient to manage. Since the follicle is difficult to remove completely, comedones may recur between 25 and 50 days following expression. Fewer than 10% of comedone extractions are a complete success, but the process is useful when done properly.[31]

Comedo removal may be helpful in the management of comedones resistant to other therapies. While the procedure cannot affect the clinical course of the disease, it can improve the patient's appearance, which may encourage adherence with the treatment program.

Ultraviolet Light

Although ultraviolet light was recommended in the past for desquamation, the practice is no longer advisable because of the well-established carcinogenic and photoaging effects of ultraviolet exposure. Moreover, inflamed skin is more susceptible to the damaging effects of ultraviolet light. Patients taking tretinoin may show heightened sensitivity.[52]

Before exposure to sunlight, patients with acne should apply sunscreens (sun protection factor [SPF] 15) in alcohol- or oil-free bases and avoid using the acnegenic benzophenones. Sunscreen should be applied as the first product.

Prevention of Cosmetic Acne

Persistent low-grade acne is frequently caused by heavy cosmetic use in women after their mid-twenties. Adolescent acne in younger women may be exacerbated with makeup overuse. The problem is perpetuated when resultant blemishes are concealed with more cosmetics.

Patients should be advised to discontinue oil-containing cosmetics and avoid cosmetic multistep regimens applying various cream-based cleansers and cover-ups. These are commercially advertised and often available with promotional bonuses through Internet shopping. Three-step basic systems usually combine medicated and nonmedicated ingredients. The product names used in marketing these preparations may not make apparent the inclusion of therapeutic agents. Initial steps usually involve cleansers, in lotions or creams, which may contain a multitude of unnecessary ingredients, including medicated peelers, oils, fragrances, and preservatives. Active ingredients including salicylic acid, sulfur, or benzoyl peroxide are often included in subtherapeutic or low doses. The second step is generally a water- or alcohol-based “toner” or “refresher,” which might contain medicated mild comedolytic agents such as α-hydroxy acids (eg, glycolic acid), or even a humectant such as glycerin. The final product, often called intensive or repairing solutions, usually contains the lowest strength of peelers such as benzoyl peroxide, sulfur, or salicylic acid; plus potentially sensitizing fragrances and preservatives; or oil-soluble sunscreens not identified on the label. Bases may have significant oil content. There may be additional products such as masks or spot treatments that supplement the base routine of three steps. Multiple-step cosmetic programs are often costly and should be avoided in favor of simple cleansers and more effective single-ingredient peelers at optimal concentrations.

The term *noncomedogenic* may refer to either water-based vehicles or products that are free of substances known to induce comedones. They are not necessarily oil-free. Water-based cosmetics may contain significant amounts of oil in the form of undiluted vegetable oils, lanolin, fatty acid esters (butyl stearate, isopropyl myristate), fatty acids (stearic acid), fatty acid alcohols, cocoa butter, coconut oil, red veterinary petrolatum, and sunscreens containing benzophenones. Water-based products are more likely to contribute to pore blockage than oil-free products.

Oil-free makeups are well tolerated and lipstick, eye shadow, eyeliner, eyebrow pencils, and loose face powders are relatively innocuous. Heavier, oil-based preparations, particularly moisturizers and hairsprays, clog pores and accelerate comedone formation.[53]

Patients should restrict cosmetic use including makeup, moisturizers, or sunscreens to products labeled oil-free rather than water-based. Cover-up cosmetics for acne are available in several skin tones and in lotion and cream forms. They often contain peeling agents, antibacterial agents, or hydroquinone. Most contain sulfur. They may be applied as cosmetics two or three times daily, over the entire face or to individual lesions. Because the spread time of oil-free makeup is decreased, best results are achieved if applied to one-quarter of the face at a time. Topical medication should be applied after gentle cleansing and a foundation lotion may be used sparingly as a concealer.[54-56]

Because the action of most therapeutic acne agents is to dry the skin, the use of nonspecific moisturizers is counterproductive. Active agents, such as α-hydroxy acids (glycolic, lactic, pyruvic, and citric acids), may be present in a cosmetic formulation, since they reduce corneocyte adhesion.[57] Patients with acne should be restricted to oil-free α-hydroxy acid products unless necessary because of treatment with strong drying agents or isotretinoin.

Cosmetics, if correctly prescribed, may improve the performance of the therapy, whereas incorrect procedures and/or inadequate cosmetics may worsen acne. Clinicians should make informed decisions about the role of various cosmetics and to identify the appropriate indications and precautions. The choice of the most effective product should take into consideration the ongoing pharmacologic therapy and acne type/severity as well.[58]

Vehicles

Topical medication is a staple in treating mild-to-moderate acne because it is an efficient way to deliver medication to the site of action and involves decreased risk of exposure to ingredients. Since local irritation from the vehicle can lead to poor adherence and outcomes, it is essential to choose a vehicle which is effective and well tolerated. Topical agents are absorbed primarily through passive diffusion via appendageal transcellular or intracellular pathways. As the active drug travels, it may undergo chemical changes in the skin or by the vehicle.[59]

The formulation of an acne vehicle must consider the technical characteristics of maintaining and delivering the drug in an active state together with the need for an elegant product that is well tolerated and the patient will enjoy using, so that it is more likely to be applied as required and deliver the full benefit. Physically and chemically, the vehicle will be used with one or more of the following goals: reduce excess oil, control bacteria associated with acne, reduce the effects of hyperkeratinization, and unclog pores. Performance, safety, and stability should be maximized while addressing technical and commercial factors.

Immiscible liquids might be delivered in oil-in-water or water-in-oil emulsions. In addition to having undesirable oil content, these vehicles also contain humectants, thickeners, preservatives, and fragrance, all of which may be problematic.

Solutions are simpler formulations. They are often used as the soaking liquid for fibrous cloth wipe products. The shelf life depends upon whether multiple wipe packages are resealable, and whether the solvent volatility will affect storage and active agent availability or cause crystallization. Solutions are used mainly with topical antibiotics, which are often dissolved in specific types of alcohol. Although some antibiotics are only soluble in ethyl alcohol, isopropyl alcohol is generally better able to remove oil from the skin surface and is preferred for nonmedicated vehicles. Solutions and washes can be more easily applied to large areas such as the back.[60] Nongreasy solutions, gels, lotions, and creams should be selected as bases for topical acne preparations. Lotions and creams will contain some oil-phase ingredients. Discourage moisturizers and oil-based products. Lotions are slightly less drying than gels, and creams are more emollient. Gels are very useful as they are mixtures of water or alcohol and totally oil free. Many gels contain ethanol or isopropyl alcohol. Propylene glycol is sometimes present in small amounts to add viscosity and lessen the drying effects of strong peeling agents. Gels are drying but may cause a burning irritation in some patients and may prevent certain kinds of cosmetics from adhering to the skin.[53] Propylene glycol gels are easy to apply and dry without a visible or sticky film. Nonalcoholic gels may be so effective and less drying than alcoholic solutions. Alcoholic or acetone gels are usually more drying and provide better penetration of the active ingredient.

Consider the patient's skin type and preferences in the choice of vehicle for topical agents. Patients with oily skin often prefer vehicles with higher proportions of alcohol (solutions and gels), while those with dry or sensitive skin prefer nonirritating lotions and creams. Hydrating and emollient products are often recommended to patients using drying treatment therapies, such as isotretinoin, to control adverse effects and improve adherence to treatment. Lotions can be used with any skin type and can be easily spread over hair-bearing skin, but they will cause burning or dryness if they contain propylene glycol. Compatibility of vehicles and agents with cosmetics should also be considered.

The focus of innovation has been optimal formulations of problematic drugs. A fixed topical alcohol-free aqueous gel combination of clindamycin phosphate 1.2% and tretinoin 0.025% given once daily simplifies administration and encourages adherence. Creamy wash and gel hydrophase options for benzoyl peroxide reduce the irritation of this drug.[61]

The importance of vehicle effects in topical therapy has been demonstrated in placebo effect literature.[61] The percent contribution of vehicle (placebo) toward efficacy of reduction of lesions counts of eight commonly prescribed topical preparations at the end of 10 to 12 weeks of daily administration has been reported as a mean value of 55% (range 35%-82%).

How to Use Topical Preparations

Topical preparations should not be applied to individual lesions but to the whole area affected by acne to prevent new lesions from developing. Care should be advised in applying around the eyelid, mouth, and neck (to avoid chafing). Lotions should be applied with a cotton swab once or twice a day after washing or at bedtime if they leave a visible residue. Skincare products may cause skin dryness and redness particularly at the early stages of the treatment. Should this occur, the product should be applied more infrequently, the treatment should be stopped for a while or another topical product tried. To reduce irritation a topical vehicle with high water content may be applied over the medicinal product after a few minutes; the irritation usually subsides as the skin becomes accustomed to the topical skincare product.

Psychologic Approaches, Hypnosis, and Biofeedback

The psychologic effects of acne may be profound. The American Academy of Dermatology expert workgroup unanimously concluded that effective acne treatment can improve the emotional outlook of patients.[62] There is weak evidence of the possible benefit of biofeedback-assisted relaxation and cognitive imagery.[63,64]

Dressings

A pilot double-blind, randomized study of 20 patients has shown some benefit of treatment with a hydrocolloid acne dressing when compared with tape dressings for improving mild-to-moderate inflammatory acne vulgaris. Results showed greater reduction over 3 to 7 days in the overall severity of acne and inflammation, along with greater improvement in redness, oiliness, dark pigmentation, and sebum casual level. Less ultraviolet B light reaches the skin surface with the hydrocolloid dressing in place.[65,66]

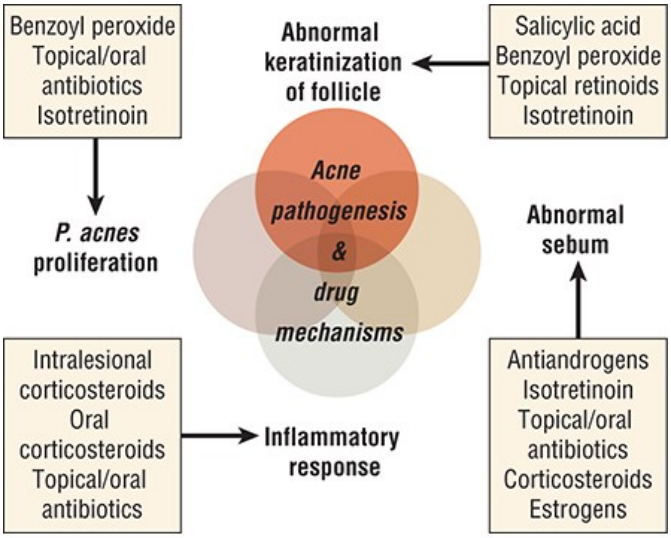
Pharmacologic Therapy

Successful pharmacologic therapy must address one of the four mechanisms involved in the pathogenesis of acne. Numerous agents are available that prove one or more of these actions and are therefore effective. However, the choice of active pharmacologic therapy depends on severity.

Mechanisms of drug action relating to acne pathogenesis are illustrated in Fig. 117-2.

FIGURE 117-2

Acne pathogenesis and drug mechanisms.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Drug Treatments of First Choice

There is concordance among key opinion leaders in different settings regarding recommendations for drugs of choice for management of acne—the Global Alliance 2018 and the 2016 European Guidelines.[24,32,67]

Managing Acne

For comedonal, noninflammatory acne Active agents of first choice include those that correct the defect in keratinization by producing exfoliation most efficaciously. Topical retinoids, in particular, adapalene, or a fixed combination with a retinoid (eg, adapalene plus benzoyl peroxide) can be recommended as drugs of choice.[24,32] Benzoyl peroxide or azelaic acid or salicylic acid can be considered, as alternatives (lower strength

recommendation).[24,32] Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first-line therapy (eg, financial resources and reimbursement limitations, legal restrictions, availability, drug licensing). Because the comedone is the initial lesion even in inflammatory acne, these agents are used to correct the defect in keratinization in all cases of acne.

For mild-to-moderate papulopustular inflammatory acne It is important to reduce the population of *P. acnes* in the follicle and the generation of its extracellular products and inflammatory effects. Either the fixed-dose combination (adapalene and benzoyl peroxide) or benzoyl peroxide or topical retinoid or azelaic acid is strongly recommended as first choice therapy (high strength recommendation).[24,32,67] In case of more widespread disease, for the treatment of **moderate papulopustular inflammatory acne**, the fixed-dose combination is preferred, with or without hormonal therapy and/or antibiotic, particularly if the trunk is involved.[67]

Low-strength recommendations are offered as considerations for treatment if there are limitations that apply in selecting a first-choice agent. The choices would be blue light monotherapy, alternate combination therapy (such as fixed-dose combination of erythromycin and tretinoin, fixed-dose combination of isotretinoin and erythromycin) or oral zinc. In case of more widespread disease, a combination of a systemic antibiotic with either benzoyl peroxide or with adapalene in fixed combination with benzoyl peroxide can be considered.[24,32]

For moderately severe or severe papulopustular or moderate nodular acne The fixed-dose combination with an oral antibiotic is preferred. Alternatively, oral isotretinoin or oral hormonal therapy can also be added.[68] If there are limitations to use these agents, considerations could be given to oral antiandrogens in combination with oral antibiotics or topical treatments, or systemic antibiotics in combination with benzoyl peroxide (low strength recommendation).

Managing Very Severe Acne

For nodular or conglobate acne In males, monotherapy with oral isotretinoin is strongly recommended as the drug of first choice (high strength recommendation).[24,32] As alternative agents, a retinoid fixed combination or oral antibiotics can be recommended. For females, oral isotretinoin plus antiandrogenic hormonal therapy is preferred. Alternatively a fixed combination retinoid with oral antibiotics (consider high dose) and/or oral antiandrogenic hormonal therapy can be recommended.[68]

For maintenance therapy for acne The most frequently recommended agents are topical retinoids or retinoid and benzoyl peroxide fixed dose combinations.[67] The most extensively studied maintenance treatment (four controlled trials) has been adapalene regimens.[24,32] Other published options include tazarotene or tretinoin. In general, maintenance therapy is begun after a 12-week induction and continues for 3 to 4 months. Continuing improvement using this schema is achieved, with relapse occurring when patients stop treatment, suggesting a longer duration of maintenance therapy is likely to be beneficial. Topical azelaic acid is an alternative to topical retinoids for acne maintenance therapy, with advantageous efficacy and safety profiles for long-term therapy. To minimize antibiotic resistance, long-term therapy with antibiotics is not recommended as an alternative to topical retinoids. If an antimicrobial effect is desired, the addition of benzoyl peroxide to topical retinoid therapy is preferred.

Published Guidelines

In general, recommendations should be based on critical appraisal and interpretation of the literature combined with clinical experience. There is considerable heterogeneity in the acne literature. The large number of products and product combinations, and the scarcity of comparative studies, has led to disparate opinions and few recommendations are evidence based. Various evidence-based guidelines, available from multiple American, Canadian, European, Scandinavian, and South African sources from 2005 to 2018, do not provide concordance or clarity on all issues.

The 2016 European Guidelines for the Treatment of Acne focus primarily on major treatments, but do not review general management issues such as psychologic determinants, scarring, and diet.[24,69] Where relevant, specific information from multiple sources will be integrated into the therapy section that follows.

An expert committee of the American Academy of Dermatology redefined guidelines for acne therapy in 2016 (Table 117-1).[68] These guidelines address the management of adolescent and adult patients presenting with acne but not the consequences of disease, including the scarring, postinflammatory erythema, or postinflammatory hyperpigmentation. In 2009, the Global Alliance to Improve Outcomes in Acne updated their 2003 recommendations to

review new information about pathophysiology and treatment and included current published data on relevant issues.[70] In 2018, the Global Alliance published a further update providing relevant clinical guidance to healthcare practitioners managing patients with acne, with an emphasis on areas where the evidence base may be sparse or needs interpretation for daily practice. They provided 10 consensus recommendations, based on the 2016 American Academy and European Guidelines.[67]

TABLE 117-1

Evidence Chart for Recommendations for Managing Acne Vulgaris

Recommendation	Strength of Recommendation	Level of Evidence
Grading/classification system	B	II, III
Microbiologic testing	B	II, III
Endocrinologic testing	B	I, II
Topical therapies		
Benzoyl peroxide	A	I, II
Topical antibiotics (eg, clindamycin, minocycline, and erythromycin)	A	I, II
Combination of topical antibiotics and benzoyl peroxide	A	I
Topical retinoids (eg, tretinoin, adapalene, tazarotene, and trifarotene)	A	I, II
Combination of topical retinoids and benzoyl peroxide/topical antibiotic	A	I, II
Azelaic acid	A	I
Dapsone	A	I, II
Salicylic acid	B	II
Systemic antibiotics		
Tetracyclines (eg, doxycycline, minocycline, and sarecycline)	A	I, II
Macrolides (eg, azithromycin and erythromycin)	A	I
Trimethoprim (with or without sulfamethoxazole)	B	II
Limiting treatment duration and concomitant/maintenance topical therapy	A	I, II
Hormonal agents		
Combined oral contraceptives	A	I
Spironolactone	B	II, III
Oral corticosteroids	B	II

Isotretinoin		
Conventional dosing	A	I, II
Low-dose treatment for moderate acne	A	I, II
Monitoring	B	II
iPLEDGE and contraception	A	II
Miscellaneous therapies and physical modalities		
Chemical peels	B	II, III
Intralesional steroids	C	III
Complementary and alternative therapies (eg, tea tree oil, herbal, and biofeedback)	B	II
Role of diet in acne effect of glycemic index	B	II
Dairy consumption	B	II

Data from Reference 68.

The Alliance recommendations statements were as follows[67]:

1. Retinoids have an essential role in treatment of acne. For most patients with inflammatory acne, comedonal acne, or both, a topical retinoid plus benzoyl peroxide is first-line therapy.[24,68,69]
2. The role of antibiotics in acne therapy has changed. Neither topical nor systemic antibiotics should be used as monotherapy for acne treatment.[69,71]
3. Oral isotretinoin should be first-line therapy for very severe (cystic and conglobate) acne.[69]
4. Oral isotretinoin therapy should proceed until full clearance of acne. Additional studies are needed to define a total cumulative dose that maintains remission.
5. Acne flare with oral isotretinoin can be minimized by initiating therapy at a low dose.
6. Most patients with acne should receive maintenance therapy with a topical retinoid.
7. Azelaic acid cream 20% or gel 15% is a useful acne treatment in pregnant women and patients with acne and PIH.
8. At present, devices that use laser, intense pulsed light, or photodynamic therapy should not be considered first-line treatment for inflammatory acne.
9. A minority of women 25 years of age have acne lesions localized only to the lower face. Topical retinoids with or without benzoyl peroxide are important components in therapy of adult acne.
10. Early and effective treatment is important to minimize potential risk for acne scarring.

General Information Regarding Efficacy and Safety

The guidelines and recommendations of the American Academy of Dermatology considered the efficacy and safety of various treatments, such as topical agents, systemic antibacterial agents, hormonal agents, isotretinoin, miscellaneous therapies, complementary and alternative therapies, and dietary restriction, based on levels of evidence and best clinical practice.[68] More specific information about the efficacy and safety of each of these specific modalities is outlined below in sections on each individual agent.

Alternative Drug Treatments

Complementary and Alternative Medications People with acne often turn to complementary and alternative medicine (CAM), such as herbal medicine, acupuncture, and dietary modifications, because of their concerns about the adverse effects of conventional medicines. Although these products might be well tolerated, very limited data exist regarding their safety and efficacy.

There is increasing interest in the use of CAM as adjuvant or single therapies: in America, 7% people report using a complementary medicine, and 2% report seeing a complementary medicine practitioner.[72] Traditional Chinese medicine has been widely used to treat acne for many years, based on a diagnosis from a traditional Chinese medicine perspective according to the different syndromes of acne.

The Cochrane collaboration undertook a systematic review, reported in 2015, to assess the effectiveness and safety of any CAM in the management of acne vulgaris. This included 35 studies, with a total of 3,227 participants in parallel-group randomized controlled trials (or the first phase data of randomized cross-over trials) of any kind of CAM, compared with no treatment, placebo, or other active therapies, in people with a diagnosis of acne vulgaris. The primary outcome was improvement of clinical signs assessed through skin lesion counts. Some evidence from single studies showed low-glycemic-load diet, tea tree oil, and pollen bee venom (PBV) may have an effect reducing total skin lesion counts and acne severity scores. However, small sample sizes and poor methodological quality limited the strength of the evidence. Evidence from other existing randomized controlled trials does not support the use of herbal medicine, acupuncture, or wet-cupping therapy for the treatment of acne vulgaris. The evidence for a secondary outcome (number of participants with remission) for herbal medicine versus antibiotic was uncertain. Two trials reported QOL showed the benefit of herbal medicine compared with western drugs. From the review of 31 studies, the Cochrane review cautioned there is a lack of evidence to support the use of other CAMs, such as aloe vera, copaiba essential oil, dried fruit of *Berberis vulgaris*, or seaweed oligosaccharides for the treatment of this condition. Most studies were done in a traditional Chinese medicine context; therefore, results might be less generalizable to western medicine. The review highlights potential adverse effects from herbal medicine (dizziness, dry mouth, nausea, diarrhea, or stomach upset); acupuncture (pain, itchiness, or redness); and tea tree oil gel (pruritus, dryness, burning sensations, and skin flaking).[73]

A 2018 review focused on the use of essential oils and aromatherapy in acne, examining existing evidence from small pilot studies.[74] It reaffirmed there is only weak clinical evidence that tea tree oil 5% may be used as an alternative acne therapy. Several agents may be helpful as complementary therapy due to biologic plausibility, including lactobacillus-fermented *Chamaecyparis obtuse*, copaiba, sandalwood oil, rosemary extract, jeju essential oil, and Korean citrus, but concluded there is little supportive clinical evidence.

The use of botanical preparations that are nonstandardized should be discouraged in favor of traditional quality-controlled preparations that have evidence of efficacy. The lack of appropriate data, absence of quality assessment, and inconsistencies in search methodology suggest that CAM cannot be recommended for acne therapy now.

Glycolic Acid

Another agent considered alternative therapy for acne vulgaris is glycolic acid. The efficacy and tolerability of a 0.1% retinaldehyde/6% glycolic acid combination (Diacneal) has been evaluated for mild-to-moderate acne vulgaris.[75] Physician and patient ratings of acne symptom severity and tolerance performed at baseline and months 1, 2, and 3 showed mean numbers of papules, pustules, and comedones were significantly reduced from month 1 on, demonstrating that glycolic acid is effective and well tolerated in mild-to-moderate acne vulgaris.

Both glycolic acid–based, salicylic acid or salicylic acid derivative–based (eg, lipohydroxyacid), and amino fruit acid–peeling preparations have been used in the treatment of acne. There is very little evidence from clinical trials published in peer-reviewed literature supporting the efficacy of peeling regimens.[62] Topical corneolytics, including retinaldehyde/glycolic acid or lactic acid, induce a comedolytic effect and may also facilitate skin absorption of topical drugs.[58] Further research on the use of peeling in the treatment of acne needs to be conducted to establish best practices for this modality.

Hydroquinone

To control pigmentation, hydroquinone, which reversibly damages melanocytes, has been used as a hypopigmenting agent in concentrations of 2% to 4%, in preparations of clear or tinted gels, which are more drying, and as vanishing or opaque, flesh-tinted creams, with or without α-hydroxy acids or sunscreens. Hydroquinone causes fading of epidermal but not dermal pigmentation. Onset of response is usually 3 to 4 weeks, and the depigmentation lasts for 2 to 6 months but is reversible. While effective in the removal of melanin, hydroquinone has been clinically found to be a possible carcinogen and causes a blue-black discoloration known as ochronosis.[76]

After considering new data and information on the safety of hydroquinone, the FDA issued a proposed ruling in 2006 about hydroquinone products. The FDA proposed reversing earlier rules that hydroquinone is generally recognized as safe and effective. The FDA has not yet issued a final ruling on the status of nonprescription hydroquinone, and many physicians consider a ban unnecessary, given the lack of convincing evidence of carcinogenic risk to humans and the rarity of ochronosis occurrence.

Treatment of Scarring

Drug and nondrug measures for scar resolution are important in acne vulgaris because many patients are scarred despite adequate treatment and scarring carries an emotional toll. Interventions for atrophic scars might be aided through early identification of patients at risk using a risk assessment tool for scar development. One such tool incorporates four factors: worst ever severity of acne, duration of acne, family history of atrophic acne scars, and lesion manipulation behaviors.[77]

Effective procedures for treatment of scarring focus on resurfacing techniques. For patients with mild scarring, nonprescription α-hydroxy acids may be used, while severe scarring may be corrected with other treatment modalities that require consultation with a dermatologist. Dermabrasion, local or subcuticular excision, collagen implants, chemical peels (eg, 70% glycolic acid, trichloroacetic acid), and laser therapy have been used to improve scarring. Atrophic scars can be treated with laser resurfacing. Usually the scar is not completely removed, but a more cosmetically acceptable result is achieved. Keloids and hypertrophic scars can be treated with intralesional triamcinolone, cryotherapy, topical steroids, and silicone sheeting. Surgical options for scars include excision, augmentation with collagen or fat, chemical peels, subcision, and injection of autologous fibroblasts.

Special Populations

About 20% of young infants (2-3 months of age) develop papules, pustules, and less commonly closed or open comedones, primarily on the cheeks, due to placental transfer of maternal androgens (neonatal acne). The acne subsides within a few months with regular maturation. Boys are affected more often than girls because of a transient increase in testosterone secretion during the third and fourth month of intrauterine life. *Malassezia* spp. may be involved in pathogenesis.[31] Resolution occurs without therapy.[78] Infants with neonatal acne may have more severe teenage acne.[31]

The treatment of acne in children is similar to treatment for adults. Because topical therapies may be more irritating in children, initiation with low concentrations is preferred. Systemic treatments should be reserved for more extensive cases. Erythromycin is preferred over tetracyclines for children younger than 9 years of age because tetracyclines can affect growing cartilage and teeth.

Although treatment with isotretinoin has numerous potential minor adverse effects in patients of all ages, an uncommon complication in young patients is premature epiphyseal closure. This generally occurs when isotretinoin is administered in high doses, thus limiting long-term therapy.

There is a growing population of women seeking acne therapy and a clinical perception that acne in women requires systemic treatment. Analyses of clinical trials have shown that topical therapy can be efficacious in this group. Most patients have an acne presentation similar to adolescent acne, with mixed inflammatory and noninflammatory lesions on multiple facial areas (not limited to the mandibular area). Topical therapy with a retinoid and antimicrobial can be a good option. Data support the use of retinoids, including adapalene/benzoyl peroxide in both 0.1% and 0.3% concentrations, tretinoin 0.04%, and a retinaldehyde 0.1%/glycolic acid/6% cream. Among antimicrobial agents, both dapsone and clindamycin/benzoyl peroxide have efficacy if a topical retinoid is added. Azelaic acid 15% gel has also shown good results in a small study. Hormonal therapy, including oral contraceptives (OCs), can play an important role in management of acne in women and is typically used in combination with topical acne therapy.[67]

Selecting appropriate treatment in pregnant women can be challenging because many acne therapies are teratogenic; all topical and especially oral retinoids should be avoided. Oral therapies, such as tetracyclines and antiandrogens, are also contraindicated in pregnancy. Topical and oral

treatment with erythromycin may be considered.

Acne in skin of color is an increasing problem, presenting unique challenges. Postinflammatory hyperpigmentation (PIH), a hypermelanotic reaction to skin inflammation, is a common occurrence in patients with acne, particularly in those with darker skin and those who excoriate their lesions, affecting all genders and ages. It has a prolonged duration and can be more bothersome than active acne lesions. Prevention (including sun protection) and early treatment of underlying acne-associated inflammation effectively is a primary approach to PIH management. Chemical peels, lasers, and other light therapies may also be used for PIH; however, these methods can also cause pigmentation problems so should be used with care. Topical retinoids also improve pigmentation by inhibiting melanosome transfer to keratinocytes and increasing epidermal turnover, lessening pigmentation. It is important for the patient to be aware that many PIH lesions resolve spontaneously, but slowly.[67]

A variety of topical agents have studies that specifically included patients with skin of color, confirming their safe use in this population. These include all the currently available topical retinoids, benzoyl peroxide, azelaic acid, clindamycin, dapsone, and clascoterone. A key goal of therapy in this population is to minimize postinflammatory hyperpigmentation from irritating topical agents, with an emphasis on use of hydrating cleansers and non-comedogenic moisturizers.[79]

Another important counseling point is to emphasize sun protective measures to minimize the darkening effects of UV irradiation on postinflammatory hyperpigmentation. Recommendations include use of a broad-spectrum sunscreen, protective clothing, and inclusion of vitamin D–rich foods or supplementation.[76]

Drug Class Information

This section reviews the pharmacology and mechanisms as related to pathophysiology for pharmacologic options recommended in the guidelines for mild, moderate, and severe acne. It will also review evidence of efficacy and safety as well as kinetics, interactions, dosing, and administration when relevant.

Topical Therapies

Topical therapy agents are available over the counter or by prescription. The choice of therapy can be influenced by age of the patient, site of involvement, extent and severity of disease, and patient preference. Topical therapies may be used as monotherapy, in combination with other topical agents, or in combination with oral agents in both initial control and maintenance. Strength of recommendations for treatment of acne with topical therapies is shown in Table 117-2.

TABLE 117-2

Monitoring of Medications Used in Acne Treatment and Maintenance Therapy

Medications	Adverse Drug Effects	Monitoring Parameters	Comments
Exfoliants			
Resorcinol	Irritant and sensitizer	Degree and/or changes in signs or symptoms of irritancy (redness, discomfort, peeling, skin breakdown, or dermatitis)	Should not be applied to large areas of the skin or on broken skin
Sulfur	Avoid eye contact—slight ophthalmic and skin irritation	Degree and/or changes in signs or symptoms of irritancy (redness, discomfort, peeling, skin breakdown, or dermatitis). Discontinue use if excessive irritation results	

Salicylic acid	Mild irritant—burning and reddening, local skin peeling	Degree and/or changes in signs or symptoms of irritancy (redness, discomfort, peeling, skin breakdown, or dermatitis)	Begin with a low concentration and increase as tolerance develops Not a sensitizer
Retinoids			
Isotretinoin	Side effects: mucocutaneous (most common), musculoskeletal, and ophthalmic systems Common: dryness of mucus membranes (lips, mouth, eyes, nose) dry skin, itching, hair loss, thirst, back pain, myalgia, headaches, and central nervous system effects Increased cholesterol Teratogenic Sun sensitivity Depression and suicide—controversial	Test for pregnancy twice before starting Contraceptive measures must be started 1 month prior, continued during the 2 months of treatment and for at least 1 month after stopping treatment (but normally 4 months) Laboratory monitoring during therapy should include triglycerides, cholesterol, transaminases, and complete blood counts (before, during, and after treatment) Degree and/or changes in signs or symptoms of irritancy to skin (redness, discomfort, peeling, skin breakdown, or dermatitis) Degree and/or changes in signs or symptoms of irritancy to mucous membranes (mouth, nose, eyes) Instances of headache or central nervous system symptoms Note prior psychiatric symptoms, monitor patients at each visit for early recognition of changes in mood or psychological well-being (before, during, and after treatment)	Drying agents must be discontinued Sun-avoidance strategies and sunscreen use recommended Vitamin A supplementation Use moisturizers (lip balm, nasal moisturizers, eye lubricants, temporary removal of contacts) Most adverse effects, such as cheilitis, and dry nose, eyes and mouth, are temporary and resolve after the drug is discontinued Advise patients about a possible risk of depression and suicidal behavior
Tretinoin/retinoic acid	Common: erythema, dryness, burning, photosensitization Rare: true contact allergy Use cautiously in pregnancy (Irritation: tazarotene > retinoic acid > adapalene)	Degree and/or changes in signs or symptoms of irritancy to skin (redness, discomfort, peeling, skin breakdown, or dermatitis) Skin changes in areas of sun exposure—dermatitis or hives	Additive effects with concomitant topical drying medications, such as products with high concentrations of alcohol, astringents, or abrasive soaps Gels and creams are less irritating than solutions Sun-avoidance strategies and sunscreen use recommended
Adapalene	Side effects include erythema, xerosis, burning and desquamation Less irritation than other retinoids	Degree and/or changes in signs or symptoms of irritancy to skin (redness, discomfort, peeling, skin breakdown,	Less photosensitivity than other agents Sun-avoidance strategies and

	Photoirritation or sensitization	or dermatitis) Skin changes in areas of sun exposure—dermatitis or hives	sunscreen use recommended
Tazarotene	Side effects include irritation, erythema, xerosis, burning, and desquamation	Skin changes in areas of sun exposure—dermatitis or hives	Contraindicated in pregnancy due to the large surface area Short contact therapy, 1-5 minutes every other night, gradually increasing to overnight advocated for dosing in patients with sensitive skin Oily complexions may tolerate twice daily, short contact time
Topical Antimicrobial Agents			
Benzoyl peroxide	Dryness and peeling appear after a few days, erythema, burning, pruritus Rare reports of contact allergic dermatitis May bleach hair and clothing Body odor, odor on clothes and bedsheets Irritation is concentration dependent—most frequent with 10% gel Irritation from gels used as vehicles—water-based < alcohol = acetone	Once tolerance is achieved, the strength may be increased to 5% or the base changed to the acetone or alcohol gels, or to paste Degree and/or changes in signs or symptoms of irritancy to skin (redness, discomfort, peeling, skin breakdown, or dermatitis) Hives	Increased skin irritation or drying effect with other medications, soaps, and cosmetics with strong drying effect Chemically incompatible with retinoic acid Cross-reactions with other sensitizers, such as Peruvian balsam, cinnamon, and other benzoic acid derivatives (topical anesthetics)
Clindamycin	Erythema, peeling, itching, dryness, and burning	Signs or symptoms of irritancy to skin (redness, discomfort, peeling, skin breakdown, or dermatitis)	
Oral Antibiotics			
Erythromycin	Gastrointestinal upset (nausea, vomiting, diarrhea) Vaginal candidiasis	If gastrointestinal adverse effects occur, monitor hydration Vaginal discharge	Drug interactions: Inhibits CYP1A2 and CYP3A4: carbamazepine, cyclosporine, theophylline, and warfarin Safe in pregnant women and children
Tetracyclines	Gastrointestinal intolerance: (tetracycline > erythromycin > doxycycline = minocycline) Vaginal candidiasis	Vaginal discharge Skin changes in areas of sun exposure—dermatitis or hives	Contraindicated in pregnant women or in children younger than 9 years of age Absorption decreased by food,

	Photosensitivity is dose-dependent (doxycycline > tetracycline)		chelated by antacids and milk To be taken on an empty stomach
Minocycline	Drug-induced lupus Pigment changes in skin, mucous membranes, and teeth Hepatitis Urticaria Dose-related dizziness (resolves with dose titration) Autoimmune hepatitis and hypersensitivity syndrome	Vaginal discharge Skin changes in areas of sun exposure—dermatitis or hives Changes or discoloration of skin, teeth, or mucous membranes Monitor degree of dizziness as dose is titrated Signs of hypersensitivity syndrome: fever, dermatitis, blistering reactions; systemic symptoms such as malaise, changes in blood pressure, or renal function	Contraindicated in pregnant women or in children younger than 9 years of age Decreased gastrointestinal absorption with Fe, Ca, Mg, Al Sun-avoidance strategies and sunscreen use recommended
Doxycycline	Gastrointestinal upset Photosensitizer (especially at higher doses)	If gastrointestinal side effects occur, monitor hydration Skin changes in areas of sun exposure—dermatitis or hives	Contraindicated in pregnant women or in children younger than 9 years of age Sun-avoidance strategies and sunscreen use recommended
Antisebum			
Combination oral contraceptives	Breakthrough bleeding, headache Serious: venous thromboembolism, hepatotoxicity	Spotting or bleeding	Oral antibiotics may decrease contraceptive efficacy—(significance controversial)
Spironolactone	Common: hyperkalemia, menstrual irregularity, gynecomastia, breast tenderness	Menstrual signs Breast changes	
Anti-inflammatory			
Azelaic acid	Primary: pruritus, burning, stinging, and tingling Other: erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis in less than 1% of patients	Skin changes in areas of sun exposure—dermatitis or hives	Adverse reactions are generally transient and mild in nature
Dapsone	Short- and long-term safety and efficacy demonstrated Peeling, dryness, and erythema	Skin changes in areas of sun exposure—dermatitis or hives	Does not induce phototoxicity or photoallergy in human dermal safety studies Medications such as rifampin, anticonvulsants, trimethoprim/sulfamethoxazole,

			and St John's wort may increase formation of dapsone hydroxylamine (toxicity)

Al, aluminum; Ca, calcium; CYP, cytochrome P450; Fe, iron; Mg, magnesium.

Exfoliants (Peeling Agents)

Exfoliants induce continuous mild drying and peeling by primary irritation, damaging the superficial layers of the skin, and inciting inflammation. This stimulates mitosis, thickening the epidermis, and increasing horny cells, scaling, and erythema. A decrease in sweating results in a dry, less oily surface and may superficially resolve pustular lesions.

In the past, a rabbit model was used to study the efficacy of topical exfoliants in retarding tar-induced comedone formation and accelerating their loss (comedolysis). In this animal model, retinoic acid (tretinoin) was most active, compared with benzoyl peroxide and salicylic acid, which were respectively less active. Data from peer-reviewed literature regarding the efficacy of sulfur, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc are limited. Traditional nonprescription exfoliants, including phenol, resorcinol, beta-naphthol, sulfur, Vleminckx solution, and sodium thiosulfate, are weak or ineffective. These agents are not comedolytic given that they affect the superficial epidermis rather than the hair canal. They have been supplanted by superior effective agents. Linoleic acid–rich phosphatidylcholine combined with 4% nicotinamide is suggested as an emulsion treatment that may be effective in normalization of follicular hyperkeratinization, and also provide anti-inflammatory effects.[80,81]

Resorcinol

Although sulfur and resorcinol have been used for many years in the treatment of acne, evidence from peer-reviewed literature supporting their efficacy is lacking.[67] The phenol derivative resorcinol is less keratolytic than salicylic acid. It is noted to be both bactericidal and fungicidal. Products containing resorcinol 1% to 2% have been used for acne, often in combination with other peeling agents such as sulfur or salicylic acid. The FDA considers resorcinol 2% and resorcinol monoacetate 3%, in combination with sulfur 3% to 8%, to be safe and effective and that the combination may enhance the activity of sulfur. However, the FDA is not convinced that resorcinol and resorcinol acetate are safe and effective when used as single ingredients, and has placed such products in category II (not generally recognized as safe and effective, or misbranded).[81]

Resorcinol is an irritant and sensitizer and should not be applied to large areas of the skin or on broken skin. It produces a reversible, dark brown scale on some dark-skinned individuals.

Protective packaging is important as resorcinol is reactive to light and oxygen. It has good solubility in both water and alcohol and is heat stabile. Thus, it is incorporated into a variety of products, including emulsions.[82]

Salicylic Acid

Salicylic acid, a β-hydroxy acid, is a comedolytic agent that is available over the counter in 0.5% to 2% strengths. Clinical trials demonstrating the efficacy or safety of salicylic acid in acne are limited, although it has been used for many years.[67] It is a natural ingredient in many plants such as willow tree or willow bark, and it penetrates the pilosebaceous unit. The comedolytic action depends on concentration: concentrations in commercial preparations (<2%-3%) are generally low. Concentrations less than 2% may in fact increase keratinization, while those between 3% and 6% are keratolytic, softening the horny layer and producing shedding of scales. Its mechanism remains unresolved, attributed to either reduced cohesion of corneocytes or shedding of epidermal cells, rather than breakdown of keratin.

Salicylic acid has no effect on the mitotic activity of normal epidermis and does not influence disordered cornification.[83] It may provide mild antibacterial value, as it is active against *P. acnes*. It offers slight anti-inflammatory activity at concentrations ranging from 0.5% to 5%. Its efficacy against comedones helps to prevent development of inflamed lesions, thus providing a delayed efficacy.[84]

Salicylic acid is effective. As a peeling agent, its relative strength compared with others in this class varies according to the model used in measurement.

It is slightly *less* potent than equal-strength benzoyl peroxide when measured with the rabbit ear animal model, and slightly *more* potent when measured with a biologic microcomedone model.[84] Its anti-inflammatory properties may help dry inflammatory lesions.[82] Its comedolytic properties are considered less potent than topical retinoids. It is often used when patients cannot tolerate a topical retinoid because of skin irritation.[85]

Its keratolytic effect may enhance the absorption of other agents. Salicylic acid is a mild irritant and may cause some degree of local skin peeling and discomfort (burning or reddening). It is not a sensitizer. Although the FDA recognizes salicylic acid as safe and effective, the compound offers no advantages over more modern topical agents such as benzoyl peroxide.[81,83,85]

Salicylic acid products are often used as first-line therapy for mild acne because of their widespread availability without a prescription in a variety of formulations. Both wash-off and leave-on preparations are well tolerated. Lower concentrations are sometimes combined with sulfur to produce an additive keratolytic effect. Concentrations up to 5% to 10% can be used for acne, beginning with a low concentration and increasing as tolerance to the irritation develops. However, the maximum strength allowed in nonprescription acne products is 2%. In high concentrations of 20% to 30% in hydroethanolic vehicles, salicylic acid, either alone or in combination, can be used as a peeling agent for comedonal acne and hyperpigmentation. It extrudes closed and open comedones several days after peel, but it must be applied under strict control to offer this adjunctive benefit when treating acne vulgaris.[86]

Sulfur

Sulfur medications often lessen the severity of acne, presumably because of keratolytic and antibacterial action. Sulfur helps to resolve comedones by an exfoliant action. Its popularity is due to its ability to quickly resolve pustules and papules, mask and conceal lesions (as a thick foundation lotion), and produce irritation leading to skin peeling and mild antibacterial action. Sulfur is used in the precipitated or colloidal form in concentrations of 2% to 10%, because it is practically insoluble in water and must be well dispersed. Its stability depends on effective maintenance of the dispersion.[82] Sulfur compounds (eg, sulfides, thioglycolates, sulfites, thiols, cysteines, and thioacetates) are also available and somewhat weaker. Sulfur can cause slight ophthalmic and dermatologic irritation, and patients should be cautioned to avoid eye contact. Use should be discontinued if excessive irritation results. Although it is often combined with salicylic acid or resorcinol to increase its effect, its use is limited by its offensive odor and the availability of more effective agents.[87]

Topical Retinoids

Topical retinoids are prescription vitamin A derivatives with well-documented, randomized, double-blind, placebo-controlled trials supporting their use for acne treatment.[68] Multiple agents are available in a variety of strengths and formulations: tretinoin, adapalene, tazarotene, and trifarotene. Each retinoid binds to a different set of retinoic acid receptors conferring slight differences in activity, tolerability, and efficacy: tretinoin to alpha, beta, and gamma; tazarotene and adapalene, selectively, to beta and gamma; and trifarotene to gamma. Binding to specific nuclear receptors reduces inflammation, and inhibits sebocyte proliferation and differentiation, which reduces sebum production.

Retinoids are the most powerful available peeling agents since normal epithelial cell differentiation is a vitamin A–dependent process. There is no consensus about the relative efficacy of currently available topical retinoids and oral isotretinoin. They are the core of topical therapy because of their ability to target key stages in the development of the disease: they are comedolytic, resolve the precursor microcomedone lesion, and are anti-inflammatory.

Retinoids act to reduce obstruction within the follicle and therefore are useful in the management of both comedonal and inflammatory acne. As a group, they are highly active peelers as they reverse abnormal keratinocyte desquamation.[88] They improve acne vulgaris by inhibiting microcomedone formation, diminishing the number of mature comedones and subsequently, inflammatory lesions. They also normalize follicular epithelium maturation and desquamation. Topical retinoids, unlike isotretinoin, do not decrease production of sebum, but primarily decrease inflammation, normalize keratinocyte differentiation, and increase keratinocyte proliferation and migration.[88]

Retinoids also facilitate acne lesion clearance through secondary effects of loosening and decreasing corneocytes. This increases skin permeability, facilitates absorption of other agents, such as antimicrobials or benzoyl peroxide, and increases penetration of oral antibiotics into the follicular canal. As a result, the overall duration of antibiotic treatment decreases, and the possibility of resistance lessens. Therefore, combination products with oral or topical antimicrobials are available for increased efficacy, faster onset of effects, decreased total antibiotic use and risk of resistance, and shorter

duration of treatment.[88] Retinoids may also improve and prevent postinflammatory hyperpigmentation often seen in people with darker complexions who have acne.

Retinoic acid (vitamin A acid or tretinoin) is a powerful exfoliant that slows the desquamation process, reducing numbers of both microcomedones and comedones.[26] Gels and creams are less irritating than solutions.

Stable and fast acting, adapalene has significant anti-inflammatory and comedolytic properties.[88-92] It causes epidermal and follicular epithelium hyperplasia, increased desquamation, keratinocyte differentiation, and loosening of corneocyte connections. Its anti-inflammatory effect is due to the inhibition of oxidative metabolism of arachidonic acid and inhibition of chemotactic reponses.[92] It is better at reducing inflammatory lesions and total lesion count[91] and causes less local irritation because of its mechanisms and receptor specificity than tretinoin or tazarotene.[90-96] Release from lotions and hydroalcoholic gels is more effective than from creams and aqueous gels and a microsphere gel formulation may be less irritating.[88,93] It is a good first-line therapy for colder climates or in patients with sensitive skin.[76]

Adapalene is generally regarded as effective but less irritating than other topical retinoids.[54,70] It is available in fixed-dose combinations in specialized gel vehicles with benzoyl peroxide to increase the efficacy in comparison with monotherapies. This strategy allows for the synergy of adapalene effects on normalizing desquamation with reduction of inflammation due to benzoyl peroxide action against *P. acnes.* Adapalene gel 0.1% is approved in the United States as a nonprescription product for once-daily application by patients aged 12 years and older.

Tazarotene has superior efficacy to parent retinoids, reducing both noninflammatory and ILs. While its exact mechanism is unknown, it is thought to activate retinoid receptors and thereby affect keratinocyte differentiation, and inhibit proinflammatory transcription factors to decrease cell proliferation and inflammation.[47] It penetrates skin but accumulates in the upper dermis. It is as effective as adapalene in reducing noninflammatory and IL counts when applied half as frequently. Compared with tretinoin, it is as effective for comedonal and more effective for inflammatory lesions when applied once daily. Tazarotene foam 0.1% can be used as an alternative vehicle to the gel with less systemic absorption and is a safe and effective formulation.[87,97,98] Tazarotene is not degraded by sunlight.[26]

Trifarotene is a topical selective agonist of RAR-γ, a receptor expressed in skin and not in internal organs. It was evaluated in two vehicle-controlled, 12-week, randomized double-blind studies of more than 2,000 patients aged 9 years and older, with 20% to 30% decrease in both noninflammatory and inflammatory lesions on the face and trunk. In an open-label extension of continued use, more than 70% of patients achieved an Investigator Global Assessment score of 0 or 1 by 52 weeks. It is approved in the United States as a once-daily application to the trunk and face in patients 9 years and older.[99]

Isotretinoin is a systemic retinoid that is reviewed separately below.

Retinoids tend to produce remissions that are maintained for extended periods of time, provided the accompanying irritation does not impede patient adherence. Side effects, including dryness, peeling, erythema, and irritation, can be mitigated by reduced frequency of application. Given any single agent, higher concentrations may be more efficacious, but with greater side effects. The vehicle of any particular retinoid may also decrease tolerability.[91,92] Most retinoids are unstable and insoluble in water.

Topical retinoids should be used cautiously in pregnancy and tazarotene is contraindicated. Tretinoin and adapalene are in FDA category C, while tazarotene, based on large-surface-area use in psoriasis (see Chapter 118, “Psoriasis”), is in FDA category X.[31] Trifarotene should be avoided in pregnancy. Cases of birth defects in the babies of females using trifarotene have been reported, as has adverse effects in pregnant rabbits given trifarotene orally during the period of organogenesis. The drug is also present in the breast milk of rats being fed the medications, and the manufacturer therefore recommends caution, with application only to small areas that would be unlikely to result in systemic absorption and avoidance of application to the nipples.

Skin type and age may influence tolerability in addition to the choice of vehicle. Oily skin may be more resistant, and darker skin is more prone to postinflammatory hyperpigmentation due to retinoid dermatitis. To decrease irritation, start with the lowest concentration and increase as tolerated. Application of retinoids should be at night, a half hour after cleansing, starting with every other night for 1 to 2 weeks to adjust to irritation. Short contact time starting with 2 minutes and adding 30 seconds per dose can be advised for patients with sensitive skin or in the winter, discontinuing and resuming after a 3-day rest if undue irritation results. Doses can be increased after 4 to 6 weeks if there is no irritation. Gels and creams are less

irritating than solutions.

Some formulations of tretinoin are not photostable and should be applied in the evening. Tretinoin also may be oxidized and inactivated by the coadministration of benzoyl peroxide. It is recommended that the two agents be applied at different times. Tretinoin microsphere formulation, adapalene, and tazarotene do not have similar restrictions. Topical retinoids have been associated with an increased risk of photosensitivity; concurrent daily sunscreen can be used to reduce the risk of sunburn.

Adapalene and tazarotene are photo-irritants (not photosensitizers), and sun avoidance and sunscreen use are imperative.[88]

These agents enhance any other topical acne regimen and allow for maintenance of clearance after discontinuation of oral therapy. Since retinoids are ideal for comedonal acne, when used in combination with other agents, they can address all acne variants. Adapalene is available in combination with benzoyl peroxide, and tretinoin is available combined with clindamycin phosphate 1.2%/tretinoin 0.025% gel, approved for those age 12 years or older.[67]

The therapy of acne in children younger than 12 years of age with products approved by the FDA has expanded. Fixed combination benzoyl peroxide 2.5%/adapalene 1% gel and trifarotene are approved for patients 9 years of age or older, and tretinoin 0.05% micronized tretinoin gel for patients 10 years of age or older. All other retinoids are approved by the FDA for patients 12 years of age or older. Current data show that retinoids in younger patients are effective and are not associated with increased irritation or risk.[67]

Overall, topical retinoids are the cornerstone of acne treatment and provide safe, effective, and economical means of treating all but the most severe cases of acne vulgaris. They should be the first step in moderate acne, alone or in combination with antibiotics and benzoyl peroxide, reverting to retinoids alone for maintenance once adequate results are achieved. Their lack of effect in inducing bacterial resistance enables long-term maintenance of remission.

Antibacterial Agents

Choices for antibacterial therapy include benzoyl peroxide, prescription topical and systemic antibiotics, and combination products. These drugs kill *P. acnes* and inhibit the production of proinflammatory mediators by organisms that are not killed.[26]

Benzoyl Peroxide

Benzoyl peroxide is a bactericidal agent that has proven effective in the treatment of acne. It kills *P. acnes* through the release of free oxygen radicals and is also mildly comedolytic. No resistance to this agent has been reported, and the addition of benzoyl peroxide to regimens of antibiotic therapy enhances results and may reduce resistance development.

Benzoyl peroxide is a derivative of coal tar and was first used for acne vulgaris in the mid-1960s, becoming popular once stable formulations aimed at its heat-lability were developed in the mid-1970s.[95] These preparations are the single most useful group of topical nonprescription drugs. Used alone or in combination, benzoyl peroxide is the standard of care for mild-to-moderate papular-pustular acne. It is an agent of first choice when combined with adapalene for most patients with mild-to-moderate inflammatory acne vulgaris and a second choice alternative for patients with noninflammatory comedonal acne.[24,32,67] A systematic review of 22 trials using benzoyl peroxide for acne vulgaris provided evidence that it reduces acne-lesion count, although high-quality evidence is not robust enough for firm conclusions.[100]

Benzoyl peroxide is well absorbed through the stratum corneum and concentrates in the pilosebaceous unit.[101] It has three principal actions useful in both noninflammatory and inflammatory acne. It produces powerful anaerobic antibacterial activity due to slow release of oxygen, thereby acting against gram-positive and gram-negative bacteria, yeasts, and fungi. This nonspecific antibacterial mechanism does not induce resistance with long-term use.[101] It has a rapid (within 2 hours) bactericidal effect that lasts at least 48 hours. As a result, it may decrease the number of inflamed lesions within 5 days. As an indirect effect, it induces suppression of sebum production; it does not reduce skin surface lipids, but is effective in reducing free fatty acids, which are comedogenic agents and triggers of inflammation.[101] Topical benzoyl peroxide 5% lowers free fatty acids 50% to 60% after daily application for 14 days and decreases aerobic bacteria by 84% and anaerobic bacteria (primarily *P. acnes*) by 98%.

Benzoyl peroxide is also comedolytic. While earlier rabbit model studies showed a benzoyl peroxide effect greater than that of salicylic acid, these

animal comedones were not physiologic but induced by tar. More recent studies using native microcomedones show an anticomedogenic effect that is only comparatively slight, compared with tretinoin or salicylic acid.[102-104]

Finally, a supplementary benefit of benzoyl peroxide is an indirect anti-inflammatory action, which is due either to its antibacterial or oxidizing effects. This has been reported in several studies and thus can be used to support treatment of predominantly inflamed lesions.[101] The drug's antiacne effect is augmented by increased blood flow, dermal irritation, local anesthetic properties, and promotion of healing.[105-108] Because the primary effect of benzoyl peroxide is antibacterial, it is most effective for inflammatory acne. Many patients with noninflammatory comedonal acne will respond to its peeling action.

Benzoyl peroxide is available in a variety of preparations without a prescription such as topical washes, foams, creams, or gels, and can be used as leave-on or wash-off agents. There is no clear superiority of different preparations in terms of effectiveness. Newer delivery systems to enhance efficacy and tolerability are also being investigated. Strengths available for acne therapy range from 2.5% to 10%. Total skin contact time and formulation can affect efficacy. Lower concentrations (eg, 2.5%-5%), water-based, and wash-off agents may be better tolerated in patients with more sensitive skin.

Cleansers containing benzoyl peroxide are available as nonprescription liquid washes and solid bars of various strengths. The desquamative and antibacterial effectiveness in a soap or wash is minimized by limited contact time and removal with proper rinsing. Alcohol and acetone gels facilitate bioavailability and may be more effective, while water-based vehicles are less irritating and better tolerated. Paste vehicles are stiffer and more drying than ointments or creams, which facilitate absorption and allow the active ingredients to stay localized.

Concentrations of 2.5%, 5%, and 10% in a water-based gel have been compared with the vehicle alone. The 2.5% formulation is equivalent to the 5% and 10% formulation in reducing the number of inflammatory lesions. The lower strength may not be as effective a peeler compared to higher strengths, which is due to an irritancy reaction. Thus, irritant side effects with the 2.5% gel are less frequent than with the 10% gel but are equivalent to the 5% gel. The lowest concentration of benzoyl peroxide should be used for treating patients with easily irritated skin and may lessen irritation when used in combination topical therapy with comedolytic agents.

Therapy is limited by staining and bleaching of hair, bedsheets, and clothing, concentration-dependent irritation, and uncommonly contact allergy. It produces a mild primary irritant dermatitis that subsides with continued use and is more likely to occur in those with fair complexions, a tendency to irritancy, or propensity to sunburn. This irritation is dependent on the concentration and the vehicle, being higher with alcoholic gels compared with emulsion bases.[102] There are rare reports of contact allergic dermatitis. Cross-reactions with other sensitizers, notably Peruvian balsam and cinnamon, are well established. It may cross-sensitize to other benzoic acid derivatives such as topical anesthetics. Concomitant use of an abrasive cleanser may initiate or enhance sensitization.[109]

Another side effect is body odor from breakdown of the benzoyl peroxide that remains on clothing and bedsheets.

Benzoyl peroxide has been combined with prescription agents to improve efficacy, reduce dosing strengths, decrease irritation, and reduce resistance of antibiotics.[110-113]

Benzoyl peroxide is combined with topical retinoids for an antimicrobial effect or used in conjunction with an antimicrobial. It reduces the likelihood of antibiotic resistance. For long-term maintenance therapy, it is recommended as a highly efficient bactericidal agent to be added to a topical retinoid.[24,32]

The adjunctive use of clindamycin/benzoyl peroxide gel with tazarotene cream promotes greater efficacy and may also enhance tolerability. Increased tolerability might be attributed to emollients in the clindamycin/benzoyl peroxide gel formulation.[114] A patented gel formulation of benzoyl peroxide 5%/clindamycin phosphate 1% (clindamycin) containing dimethicone and glycerin was studied both as a monotherapy and in combination with topical retinoid use. Certain additives, such as silicates and specific humectants, reduced irritation by maintaining barrier integrity.[115]

When using single-agent preparations of benzoyl peroxide, the weakest concentration (2.5%) in a water-based formulation is preferred for anyone with a history of skin irritation.[115] There are many suggested routines to initiate therapy. One is to gently cleanse the skin and apply the preparation for 15 minutes the first evening, avoiding the eyes and mucous membranes. A mild stinging and reddening will appear. Each evening the time should be

doubled until the product is left on for 4 hours and subsequently all night. Dryness and peeling will appear after a few days. Once tolerance is achieved, the strength may be increased to 5% or the base changed to the acetone or alcohol gels, or to paste. Alternatively, benzoyl peroxide can be applied for 2 hours for four nights, 4 hours for four nights, and then left on all night. It is important to wash the product off in the morning. Other drying agents should be discontinued. Patients with very sensitive skin or demonstrated sensitivity to benzoyl peroxide should not use the product, and it should be discontinued if irritation becomes severe upon use. Contact with eyes, lips, or mouth should be avoided.

A sunscreen is recommended if benzoyl peroxide is used. To avoid interactions, apply the sunscreen during the day and the benzoyl peroxide at night.

Topical Antibacterials

Topical antibiotics for acne accumulate in the follicle, where they can have antibacterial effects (the primary mechanism for efficacy in acne) and anti-inflammatory actions. These agents are best used in combination with benzoyl peroxide (wash-off or leave-on), which increases efficacy and decreases the development of resistant bacterial strains. Monotherapy with topical antibiotics in the management of acne is not recommended because of the development of antibiotic resistance.[116,117] Macrolides, including topical erythromycin and topical clindamycin, are effective and well-tolerated, well-established acne treatments.

Clindamycin is available as a single agent for topical acne therapy. Topical erythromycin has reduced efficacy in comparison with clindamycin because of resistance of cutaneous staphylococci and *P. acnes*.[68] More than 50% of *P. acnes* strains are resistant to topical macrolides. Resistant strains are usually resistant to all macrolides.[118]

Current recommendations discourage topical antibiotic monotherapy in favor of combination therapy with benzoyl peroxide and topical retinoids. Addition of benzoyl peroxide or topical retinoids to the macrolide antibiotic regimen is more effective than monotherapy and mitigates against survival of resistant *P. acnes* populations.

Clindamycin is the preferred macrolide because of potent action, lack of absorption, and its systemic use is limited because it can cause pseudomembranous colitis when given orally or by injection. It is available as a single ingredient topical preparation and can also be combined with benzoyl peroxide. A topical fixed-dose clindamycin phosphate 12% and benzoyl peroxide 30% combination gel once daily was more effective and twice daily at least as effective as clindamycin alone twice daily, with an early onset of action and an acceptable safety and tolerability profile.[119] Erythromycin is available alone and in combination with retinoic acid or benzoyl peroxide. Stable, fixed-combination agents are available with erythromycin 3%/benzoyl peroxide 5%, clindamycin 1%/benzoyl peroxide 5%, and clindamycin 1%/benzoyl peroxide 3.75%. Combination agents may enhance adherence with treatment regimens. Some topical antibiotic–benzoyl peroxide combinations require refrigeration.[62] Tolerance with these agents is excellent; clindamycin alone is pregnancy category B.[68]

Other topical antibiotics that are being studied include fluoroquinolones, such as nadifloxacin and minocycline, but these are not approved for use in patients with acne by FDA. Minocycline 4% foam is approved by FDA for topical treatment of patients aged 9 years and older with inflammatory lesions of nonnodular moderate-to-severe acne vulgaris. Its use has been evaluated in 3 large randomized, double-blind, vehicle-controlled study in patients with moderate-to-severe acne. Once-daily application for 12 weeks was associated with a decrease in inflammatory lesion count of approximately 13% to 17% compared with 10% to 17% with vehicle alone. It is generally well tolerated, with the most common adverse effects including headache (3%), mild erythema (14.2%), inflammatory/postinflammatory hyperpigmentation (12.4%), and xerosis (6.8%).[120]

Minocycline is formulated in a yellow base, which can stain fabrics but does not permanently stain skin, and there are no reports to date of drug-induced pigmentation associated with topical application. There are additionally no reports to date of bacterial resistance with topical minocycline. It is broken down by benzoyl peroxide; they should be applied 8 hours apart when used concurrently.

Oral Antibacterials

Overview: a systematic evidence-based review of scientific evidence of the efficacy of oral antibiotics for acne was published in 2017. Due to heterogeneity in trials, there is insufficient evidence to support one type, dose, or duration of oral antibiotic over another in terms of efficacy and summarized key points.[121]

- The use of oral antibiotics is reserved for patients with moderate-to-severe inflammatory acne.

- Tetracyclines are considered first-line therapy, while macrolides and trimethoprim/sulfamethoxazole are acceptable alternative agents.
- It is recommended that oral antibiotics be prescribed with concurrent topical therapy for improved efficacy and to combat antibiotic resistance.
- The choice of antibiotic should be determined based on the side effect profile, resistance, cost, and consensus guidelines.
- Oral antibiotics used in the treatment of acne may have unintended effects on nontarget bacteria, and the clinical implications of this warrant further exploration.

Systemic antibiotics are a standard of care in the management of moderate and severe acne and treatment-resistant forms of inflammatory acne. There is evidence to support the use of tetracycline, doxycycline, minocycline, erythromycin, trimethoprim-sulfamethoxazole, trimethoprim, and azithromycin. Studies do not exist for the use of ampicillin, amoxicillin, or cephalexin. However, any antibiotic that can reduce the *P. acnes* population in vivo and interfere with the organism's ability to generate inflammatory agents should be effective.[62] Although erythromycin is effective, use should be limited to those who cannot use one of the tetracyclines (ie, pregnant women or children under 8 years of age because of the potential for damage to the skeleton or teeth). Ciprofloxacin, trimethoprim-sulfamethoxazole, and trimethoprim alone are also effective in instances where other antibiotics cannot be used or for patients who do not respond to conventional treatment.[81,122]

The tetracycline antibiotic family has multiple modes of action, well-understood antibacterial effects, and anti-inflammatory effects that target an additional aspect of pathogenesis.[116,122,123] Through calcium chelation, they inhibit neutrophil and monocyte chemotaxis. Concentrations below the antibiotic threshold still inhibit inflammation and improve both acne vulgaris and acne rosacea.

Tetracycline is no longer the drug of choice in this family; disadvantages include diet-related effects on absorption and the drug's lower anti-inflammatory and antibacterial activity.

The incidence of significant adverse effects with oral antibiotic use is low. However, adverse effect profiles may be helpful for each systemic antibiotic used in the treatment of acne. Vaginal candidiasis may complicate the use of all oral antibiotics.[62] Doxycycline is very commonly a photosensitizer especially at higher doses.

Minocycline has been associated with pigment deposition in the skin, mucous membranes, and teeth, particularly among patients receiving long-term therapy and/or higher doses of the medication. In some instances this is irreversible. Pigmentation occurs most often in acne scars, anterior shins, and mucous membranes. Minocycline may cause dose-related dizziness, which resolves with dose titration; urticaria; hypersensitivity syndrome, autoimmune hepatitis, a systemic lupus erythematosus-like syndrome; and serum sickness-like reactions.[62,116]

The Cochrane collaboration has conducted a review into the efficacy and safety of minocycline, examining 39 randomized controlled trials. These studies show that minocycline is an effective treatment for moderate-to-severe inflammatory acne but present no evidence to support the first-line use of minocycline in acne treatment. The drug is more lipophilic, may act more quickly, and can be taken once daily. However, people treated with minocycline are at a significantly greater risk of developing an autoimmune syndrome than those given tetracycline or no treatment.[124]

Sarecycline (Seysara) is a new, oral, narrow-spectrum tetracycline-derived antibiotic with anti-inflammatory properties. It is specifically indicated for the treatment of inflammatory lesions of non-nodular moderate-to-severe acne vulgaris in patients 9 years of age or older. The mechanism of action in treating acne vulgaris is not known. Sarecycline should be taken with or without food once daily at a weight-based tiered dosage (60 mg if 33-54 kg, 100 mg if 55-84 kg, and 150 mg if 85-136 kg). To reduce the risk of esophageal irritation and ulceration, sarecycline should be administered with adequate amounts of fluid.

The FDA approval of sarecycline in October 2018 was based on two identically designed, large, multicenter, randomized, double-blind, placebo-controlled, phase III studies that assessed use in a total of 2,002 participants 9 years of age or older with moderate-to-severe facial acne vulgaris. Data demonstrated that once-daily sarecycline 1.5 mg/kg significantly improved acne severity based on Investigator's Global Assessment (IGA) success and significantly reduced inflammatory lesion count versus placebo at week 12. Study 1: IGA success, 21.9% versus 10.5%, and mean absolute reduction in number of inflammatory lesions, 15.3 versus 10.2. Study 2: IGA success, 22.6% versus 15.3%, and mean absolute reduction in inflammatory lesions, 15.5 versus 11.1.[125-127]

Bacterial resistance to antibiotics is an increasing problem in acne therapy, particularly because treatments are used over a long period of time.[116] The development of strains with unidentified mutations suggests new evolving mechanisms of resistance. Combined resistance to clindamycin and erythromycin is much more common than resistance to tetracycline. Use of topical antibiotics can lead to resistance largely confined to the skin of treated sites, whereas oral antibiotics can lead to resistance in commensal flora at all body sites. Resistance is more common in patients with moderate-to-severe acne and in countries with high outpatient antibiotic sales. Resistance is disseminated primarily by person-to-person contact, and thus the spread occurs frequently.

There have been an increasing number of reports of systemic infections caused by resistant *P. acnes* in nonacne patients after surgery. A transmission of factors conferring resistance to bacteria other than *P. acnes* has been described.

The most likely consequence of resistance is decreased clinical efficacy of antibiotic-based treatment regimens compared with that in patients with fully susceptible flora.

Studies on *P. acnes* resistance have highlighted the need for treatment guidelines to restrict the use of antibiotics to limit the emergence of resistant strains. Patients with less severe forms of acne should not be treated with oral antibiotics, and where possible such therapy should be limited to the shortest feasible duration (eg, 6-8 weeks). Local patterns of resistance should be considered. The use of systemic antibiotics should be limited (both indication and duration) and topical antibiotic monotherapy should be avoided.

Guidelines advocate early use of combination therapy with retinoids. Often, when oral antibiotics are combined with topical agents, the antibiotic may be discontinued after 6 months of therapy. Nearly 70% of patients with acne require antibiotics for 12 weeks or less if aggressive retinoid therapy is introduced during that time.[116]

Another potential strategy is to eliminate the use of antibiotics and combine other topical agents. Neither retinoids nor benzoyl peroxide creates selective pressure for resistance and is one combination option. Although this approach has been evaluated for efficacy and safety, there is limited evidence of its effect on microbial resistance. In one open label study of adapalene and benzoyl peroxide, baseline counts of antibiotic resistant strains of *P. acnes* were reduced by week 4.[116]

Stricter cross-infection control measures are recommended when assessing acne. Any topical or systemic antibiotic therapy should be combined when possible with broad-spectrum antibacterial agents such as benzoyl peroxide. In addition, isotretinoin use should be initiated earlier in indicated patients, rather than prolonging antibiotic courses.[24,69]

Other Topical Agents

A tyrosine kinase inhibitor, azelaic acid has been used in patients with sensitive skin or of Fitzpatrick skin types IV or greater because of the lightening effect of the product on dyspigmentation.[67]

Azelaic acid possesses activity against all four pathogenic factors that produce acne. It has anti-inflammatory and antibacterial activities. Azelaic acid also normalizes keratinization, which accounts for its anticomedogenic effect. It is a competitive inhibitor of mitochondrial oxidoreductases and of 5-α-reductase, inhibiting the conversion of testosterone to 5-dehydrotestosterone. It also possesses bacteriostatic activity to both aerobic and anaerobic bacteria including *P. acnes*. Azelaic acid is an antikeratinizing agent, displaying antiproliferative cytostatic effects on keratinocytes and modulating the early and terminal phases of epidermal differentiation.[103] It may produce hypopigmentation. Inhibition of thioredoxin reductase by azelaic acid provides a rationale for its depigmenting property.

Azelaic acid 20% cream is used in the treatment of mild-to-moderate inflammatory acne, has an excellent safety profile with minimal adverse effects, and is well tolerated in comparison with other acne treatments. The most common adverse effects are pruritus, burning, stinging, and tingling; these are reported in 1% to 5% of patients. These are generally transient and mild in nature. Other adverse reactions, such as erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis, were reported in fewer than 1% of patients.

Azelaic acid has beeneffective in clinical trials studied with topical 2% erythromycin, topical 5% benzoyl peroxide gel, and topical 0.05% tretinoin cream in the treatment of mild-to-moderate inflammatory acne. However, the agent has limited efficacy, compared with other antiacne therapies.[62] It is an alternative to first choice therapy for comedonal and all types inflammatory acne, particularly in combination. It is an alternative to topical retinoids for

maintenance therapy as its efficacy and safety profile are advantageous for long-term therapy.[24,32,67]

Azelaic acid should be applied twice a day, in the morning and evening. A majority of patients with inflammatory lesions may experience an improvement in their acne within 4 weeks of beginning treatment. However, treatment may be continued over several months, if necessary.

Azelaic acid is in a pregnancy category B and should only be used in pregnant women if medically necessary. Patients with dark complexions should be monitored for early signs of hypopigmentation.

Dapsone, a synthetic sulfone, is available topically as 5% and 7.5% gels for acne, and may be used in sulfonamide-allergic patients. Dapsone's utility is attributable to its anti-inflammatory and antimicrobial properties that improve both inflammatory and noninflammatory acne, with more prominent effects occurring in inflammatory lesions. In clinical trials, topical dapsone showed modest-to-moderate efficacy, primarily in the reduction of inflammatory lesions. Short- and long-term safety and efficacy have been demonstrated.[128]

In a study of 101 adult women with mild-to-moderate inflammatory facial acne and sensitive skin for 12 weeks, topical 5% dapsone gel was effective and minimally irritating. Response to dapsone appears to be influenced by gender, with female patients experiencing a significantly greater reduction in acne lesion counts and a significantly higher clinical success rate following 12 weeks of treatment.[129]

Topical 5% dapsone gel is recommended to be used twice daily for acne. Conversely, dapsone 7.5% gel is indicated once daily. It received FDA approval for use in patients aged 12 years and older based on a pair of 12-week, double-blind, placebo-controlled, randomized trials that included more than 4,300 participants with acne. In these studies, a Global Acne Assessment Score of 0 or 1 with at least a two-grade improvement was achieved in 30% of patients assigned to dapsone 7.5% gel, compared with 21% of vehicle-treated controls. It was extremely well tolerated, with application site dryness and itching rates similar to placebo.[130]

Topical dapsone is especially beneficial for patients exhibiting sensitivities or intolerance to conventional antiacne agents.[131]

Combination therapy with dapsone and topical retinoids may be indicated if comedonal components are present. Topical dapsone 5%, alone or in combination, with adapalene 0.1% or benzoyl peroxide 4% has been safe and efficacious but may be more irritating than other topical agents.[131,132]

Intralesional Steroids

Intralesional corticosteroid injections are effective for individual inflammatory acne nodules. The effect of intralesional injection with corticosteroids (eg, triamcinolone acetonide) is a well-established and recognized treatment for large inflammatory lesions. Cystic acne improved in patients receiving intralesional steroids.[62] Rapid improvement and decreased pain are noted.

Systemic absorption of steroids may occur with intralesional injections. Adrenal suppression was observed in one study. The injection of intralesional steroids may be associated with local atrophy. Lowering the concentration and/or volume of steroid may minimize these complications.

Hormonal Agents

Two topical antiandrogen treatments are now available: clascoterone and topical spironolactone. Systemic antiandrogen agents include oral contraceptives and systemic spironolactone.

Clascoterone is an androgen receptor inhibitor with a greater ability to inhibit inflammatory cytokine synthesis from sebocytes compared to spironolactone. It has been approved in a 1% cream formulation for topical treatment of acne vulgaris in patients 12 years and older based on two randomized, double-blind, vehicle-controlled trials of 1,421 participants 12 years and older with moderate-to-severe facial acne vulgaris. Overall, 62% of participants were female, and 91% were White, with a mean age of 19.7 years. After 12 weeks of twice-daily application, clascoterone cream 1%, produced a significant reduction in absolute noninflammatory lesions from baseline to −19.4 (both trials) versus −13.0 and −10.8 with vehicle, respectively, as well as a reduction in inflammatory lesions from baseline to −19.3 and −20.0 versus −15.5 and −12.6 with vehicle, respectively. The most common side effects were erythema, pruritus, edema, stinging, and burning.[133]

In contrast to systemic spironolactone, topical clascoterone can be used in both males and females. There are no human data on use in pregnancy, but subcutaneous exposure to doses 8 to 39 times maximal recommended human doses resulted in increased malformations in rats and postimplantation

loss and resorptions in rabbits. There are no data on safety in lactation or detection of drug or metabolite in human milk.[134]

Oral Contraceptives

Estrogen-containing oral contraceptives can be useful in the treatment of acne in some women. Those approved by the FDA for the management of acne contain norgestimate with ethinyl estradiol and norethindrone acetate with ethinyl estradiol. There is good evidence and consensus opinion that other estrogen-containing oral contraceptives are also equally effective.[62]

The mechanism of action of combination oral contraceptives (COCs) in the treatment of acne is based on their antiandrogenic properties. These hormones decrease androgen production at the level of the ovary and also increase sex hormone-binding globulin, binding free circulating testosterone and rendering it unavailable to bind and activate the androgen receptor. In addition, COCs reduce 5-α-reductase activity and block the androgen receptor.[68]

The risks of COCs must be weighed against the risks of the condition that they are treating or preventing. If COCs are used exclusively for acne, their risks must be compared to the risks of acne. It is important to remember that FDA approval of all COCs for acne specifies that they are approved for the treatment of acne in women who also desire contraception. COCs carry cardiovascular risks, and breast cancer risks in some women, and low estrogen may affect bone mass. However, decreased risks of colorectal, ovarian, and endometrial cancers have been shown.

Oral contraceptives may improve acne for many women with clinical and laboratory findings of hyperandrogenism and in women without these findings.[68]

The Cochrane collaboration conducted a review in 2012 to determine the effectiveness of COCs for the treatment of facial acne compared with placebo or other active therapies. Thirty-one trials with a total of 12,579 women were reviewed.[134]

Combination oral contraceptive use reduced inflammatory and noninflammatory facial lesion counts, severity grades, and self-assessed acne in nine placebo comparison trials, according to the review.

Most studies assessed women over six treatment cycles, which might not be adequate for a chronic condition like acne. In two trials, patients were more likely to discontinue because of adverse events, suggesting even if COCs improve acne, women might not be willing to accept long-term use for acne because of other side effects.

The review concluded that COCs should be considered for women with acne who also want an oral contraceptive.

A meta-analysis review of 32 randomized controlled trials comparing use of antibiotics to oral contraceptive agents for acne concluded that although antibiotics may be superior at 3 months, oral contraceptive agents are equivalent to antibiotics at 6 months in reducing acne lesions and may be a better first-line alternative to systemic antibiotics for long-term acne management in women.[135]

Spironolactone

Spironolactone is an antiandrogenic compound that decreases testosterone production and competitively inhibits binding of testosterone and dihydrotestosterone to androgen receptors in the skin. Spironolactone may cause hyperkalemia, primarily with higher doses or in patients with cardiac or renal compromise. Routine use occasionally causes menstrual irregularity. A 5% spironolactone gel, studied in patients with increased sebum secretion, resulted in a decrease in the total acne lesions with no significant efficacy under the acne severity index.[136,137]

A single center review of 80 female patients with acne treated with systemic spironolactone (median age 19 years; range 14-20) reported complete response in 22.5% of patients, and complete or partial response greater than 50% in 58.8% of subjects. The median dose was 100 mg, and median time to initial and maximal responses were 3 and 5 months, respectively. Responders were more likely to have jawline distribution of acne (70.3% vs 56.3%) and cyclic flares (75% vs 56.3%), although this was not significant. Only three patients experienced side effects (rash, breast tenderness, diarrhea, and headache) and discontinued treatment. There were no reports of symptoms of hypotension, although blood pressure and potassium were not routinely checked in the cohort.[138]

Although not currently FDA approved for the treatment of acne, the 2016 AAD work group supports the use of spironolactone in the management of

acne in select women.[68]

Oral Corticosteroids

Oral corticosteroids have two potential modes of activity in the treatment of acne. One study demonstrated that low-dose corticosteroids suppress adrenal activity in patients who have proven adrenal hyperactivity.[139] Low-dose prednisone in doses ranging from 5 to 15 mg daily, administered alone or with high estrogen containing COCs, has efficacy in the treatment of acne and seborrhea. Expert opinion is that short courses of higher dose oral corticosteroids may be beneficial in patients with highly inflammatory disease. Long-term adverse effects of corticosteroids prohibit use as a primary therapy for acne.[68]

Oral Isotretinoin

Isotretinoin has been revolutionary for acne treatment. The risk of potential adverse effects must be weighed against its ability to prevent lifelong and permanent physical and psychologic scarring.[140]

Oral isotretinoin is an isomer of retinoic acid that has been used for many years and is approved by the FDA for the treatment of severe recalcitrant acne vulgaris. Its use results in decreased sebum production, acne lesions, and acne scarring, along with a decrease in symptoms of anxiety and depression. The 2016 AAD guidelines recommend use of oral isotretinoin in patients with moderate acne that is treatment-resistant or that produces physical scarring or significant psychosocial distress.

Oral isotretinoin is a natural metabolite of vitamin A. Its mechanism is elusive, as it does not bind to retinoid receptors. It reduces sebogenesis and may also inhibit sebaceous gland activity, growth of *P. acnes*, and inflammation, and improve follicular epithelial differentiation.[141] Systemic isotretinoin exerts a primary effect on comedogenesis, causing a decrease in size and reduction in formation of new comedones.[26] Isotretinoin is the only drug treatment for acne that produces prolonged remission.

The teratogenic effects of oral retinoid therapy are well documented, and it should be prescribed only by those physicians knowledgeable in its appropriate administration and monitoring. Individuals capable of becoming pregnant who are of child-bearing potential must enroll in the approved pregnancy prevention and management program (ie, iPLEDGE) to be treated with isotretinoin. Two different forms of contraception must be started 1 month before and continue at least 1 month (but normally 4 months) after therapy and pregnancy monitoring undertaken before, during, and after therapy.[140]

The efficacy of conventional isotretinoin treatment (0.5-1.0 mg/kg/day for 16-32 weeks, reaching a cumulative dose of 120-150 mg/kg) for acne has been well established. The approved dosage of isotretinoin is 0.5 to 2.0 mg/kg/day.

Initial flaring can be minimized by initiation of lower doses (ie, 0.5 mg/kg/day or less). Many reports document efficacy of low-dose and intermittent isotretinoin treatment. Lower doses can be used for longer time periods, with a total cumulative dose of 120 to 150 mg/kg or the dose can be lowered to 20 mg on alternate days after an initial 2 months of therapy with higher dosage.[142-144] Reports suggest that low-dose regimens are superior to other regimens (conventional or intermittent) in terms of patient satisfaction, tolerability, and efficacy in patients with moderate acne. In patients with severely inflamed acne, an even greater initial dose reduction may be required or pretreatment with oral corticosteroids considered.

Some patients experience a relapse of acne after the first course of treatment with isotretinoin. A retrospective review compared 82 patients who completed two courses of isotretinoin to 160 patients with only one course. Patients receiving a second course had shorter time from clear date to end of the treatment (32.0 ± 43.3 days compared with 65.4 ± 65 days).[145] Despite the small number of patients and retrospective nature of these data, waiting for 2 months without new lesions has been adopted by some practitioners to minimize risk of relapse after achieving target cumulative dosing.

The 2016 AAD guidelines support initiation of isotretinoin at 0.5 mg/kg/day when appropriate, subsequently increasing to a full dose of 1 mg/kg/day after the first month as tolerated, with a goal cumulative dose between 120 and 150 mg/kg. One recent study of 116 patients found that a cumulative dose of 220 mg/kg or more may result in lower relapse rates, but confirmation will require study in larger populations.[68]

Isotretinoin is highly lipophilic and best absorbed when taken with food. One novel formulation is less dependent on the presence of fat in the gut for

absorption.[146] When prescribed, drying agents must be discontinued and replaced with moisturizers.

Because isotretinoin is a vitamin A derivative, it interacts with many of the biologic systems of the body, and consequently has a significant pattern of adverse effects. The pattern is similar to that seen in hypervitaminosis A. Side effects include those of the mucocutaneous (most common), musculoskeletal, and ophthalmic systems, as well as headaches and central nervous system effects. Most adverse effects, including cheilitis and dry nose, eyes, and mouth, are transient and resolve with drug discontinuation.[140] Laboratory monitoring during therapy should include triglycerides, cholesterol, transaminases, and complete blood counts.

Mood disorders, depression, suicidal ideation, and suicides have been reported sporadically in patients taking this drug. A causal relationship has not been established. These symptoms are quite common in adolescents and young adults, the age range of patients who are likely to receive isotretinoin.

Issues regarding responsible and informed use Published data and expert opinion differ with respect to the use of isotretinoin as first-line or reserve therapy, optimal dosing, and risk of depression.[140]

Although some persist in reserving isotretinoin use only for severe acne, nodular or conglobate acne that has not responded to appropriate antibiotics and topical therapy, delaying use of isotretinoin, the most effective choice, poses an ethical problem.[147] Opinions vary on whether or not to restrict use to patients under 12 years and whether to avoid lasers, peelers, or wax epilation for at least 6 months after discontinuation of therapy.[148]

The causal relationship between the use of isotretinoin and risk of depression continues to be scrutinized with no consensus. The issue is complex as depression and suicidal ideation occur with severe acne in the absence of isotretinoin.

There are instances in which withdrawal of isotretinoin has resulted in improved mood, and reintroduction of isotretinoin has resulted in the return of mood changes. Treatment of severe acne with isotretinoin is often associated with mood improvement.[62] There is epidemiologic evidence that the incidence of these events is lower in patients treated with isotretinoin than in an age-matched general population. There is also evidence that the risk of depressed mood is no greater during isotretinoin therapy than during therapy of an age-matched acne group treated with conservative therapy.[62]

A 2016 review on isotretinoin controversies, facts, and recommendations concluded despite common misperceptions, there is weak evidence for increased incidence of depression, suicidality, or inflammatory bowel disease with isotretinoin use, and data indicate that transient increases in transaminases and lipid levels do not typically necessitate discontinuation of therapy.[149]

In 2017, a systematic review and meta-analysis of the literature, with 31 studies, concluded isotretinoin treatment for acne did not appear to be associated with an increased risk for depression and that the treatment of acne appears to ameliorate depressive symptoms.[150] Current literature regarding the association with depression and suicide was reexamined in 2018. It reconfirmed that while those with a personal or family history of mental disorder might be at risk, further studies are needed and no conclusions can be drawn.[151] The current literature is insufficient to support a meaningful causative association, but important study limitations exist. In the absence of definitive evidence, an idiosyncratic effect cannot be excluded. This disputed association remains an important area for future research. Given the prevalence of depression, anxiety, and suicidal ideation/suicide in the general population, and especially the adolescent population who may be candidates for isotretinoin therapy, the prescribing physician should continue to monitor for these symptoms at each visit for early recognition, advise patients about a possible risk of depression and suicidal behavior, and make therapeutic decisions within the context of each individual patient.[68]

Light Therapy

Light therapies are believed to work by killing *P. acnes* and by damaging and shrinking sebaceous glands, reducing sebum output and have few[152] or temporary[153,154] adverse effects. Light therapies may be used once or twice weekly as a course of 6 to 10 treatments, with each irradiation lasting 10 to 20 minutes.[154] *P. acnes* produce endogenous porphyrins that absorb light to form highly reactive singlet oxygen, which destroys the bacteria.[154] There is still debate about the effectiveness of different wavelengths.[154] Since porphyrins have peak absorption at blue light wavelengths, blue light is often used to treat acne. Red light is also absorbed by porphyrins and can penetrate deeper into the skin,[155] where it may directly affect inflammatory mediators. Other light therapies attempt to selectively target and damage sebaceous glands directly, reducing their size and thus sebum output.[156] These include infrared lasers, low-energy pulsed dye lasers, and radiofrequency devices.[154]

Photodynamic therapy (PDT) uses specific light-activating creams, which are absorbed into the skin and amplify the response to light therapy but tend to produce more severe adverse effects. There are concerns that PDT may interfere with the skin's natural immune mechanisms[157,158] and cause long-term skin damage.

Light therapies, previously expensive and accessed privately via dermatologists or clinics, are increasingly popular. Home-use blue light therapy is now available. Patients find it easier to comply with light treatments because of their short duration.

Very few trials compare light therapy with conventional acne treatments. The European evidence-based guidelines concluded published evidence is scarce and standardized treatment protocols and widespread experience are lacking. Due to conflicting or insufficient evidence, these guidelines did not make a recommendation for or against treatment of comedonal, MMPP, or severe papulopustular/nodular acne with monotherapy visible light, visible or infrared wavelength lasers, or intense pulsed light or PDT. Blue light has a low strength recommendation as a consideration for MMPP.[24,69] An ongoing Cochrane review protocol continues to investigate the current state of evidence for use of light therapy in acne.[159]

Pharmacologic Cleansing Options

Medicated Soaps and Washes

Medicated soaps, washes, and foams may contain topical antiseptics such as triclosan; peeling agents such as salicylic acid, sulfur; antimicrobials such as benzoyl peroxide, clindamycin, or azelaic acid, alone or in combination in low concentrations. They may be nonprescription or prescription status.[160] Most washes should remain on the skin from 15 seconds to 5 minutes followed by thorough rinsing. This limits the amount of time the active ingredient is in contact with the skin. Other cleansers are applied after washing and left on the skin without rinsing.

Quaternary ammonium compounds are cationic detergents that are inactivated quickly in the presence of organic material such as sebum. The duration of action of these products is short.

Antiseptic cleansers that have been studied include hexachlorophene, chlorhexidine, and povidone-iodine. Use of hexachlorophene has since been banned in nonprescription products by the UFDA because of neurotoxicity concerns. Bacteriostatic soaps containing hexachlorophene, carbanilides, and salicylanilides (halogenated hydroxyphenols) may alter normal flora or be acnegenic. Few ordinary soaps induce acne. However, acne patients are particularly susceptible to comedogenic contactants, and if these soaps are applied several times daily for long periods, they may become troublesome.

Soaps containing coal tar, which can induce folliculitis, are not indicated for acne.

In a very small group of patients in an 8-week, double-blind, randomized clinical trial, a combination cleanser containing triclosan, azelaic acid, and salicylic acid produced a greater histopathologic decrease in inflammatory response compared with a nonmedicated cleanser, but there was no significant difference in noninflammatory lesions in either group.[161] A rebound tendency was noted for the nonmedicated cleanser with respect to inflammatory lesions at 4 weeks. Authors concluded that nonmedicated cleansers were an easier and cheaper way of managing patients with mild acne.

Chlorhexidine inhibits in vitro growth of *P. acnes*.[162] A 4% chlorhexidine gluconate preparation in a detergent base is as effective as benzoyl peroxide washes in patients with mild acne, and both preparations reduced the number of inflammatory and noninflammatory lesions after 8 and 12 weeks, compared with vehicle alone.[161] However, further evidence is lacking, and irritation is a side effect.[49]

Glycolic 1%, an alpha-hydroxy acid (AHA), has been used as a cleanser. AHAs cause desquamation by decreasing basal corneocyte cohesion and limiting follicular occlusion. AHA-containing formulations may be considered in the treatment of acne in light of mechanistic similarities with better validated antikeratinization agents such as retinoids.[49]

Alcohol-detergent medicated pads, impregnated with salicylic acid 0.5%, have reduced inflammatory lesions and open comedones in mild-to-moderate acne. This type of medication is less abrasive, not rinsed off, and convenient.[163]

Alcohol-detergent wipes, swabs, or "pledgets" impregnated with antibiotics, such as clindamycin or lincomycin, are available. The antibiotic is deposited in low concentrations on the surface of the skin and may not penetrate to the depths of the pilosebaceous duct. Although patients may like

the convenience and perception of using an active agent, they should not be recommended over simple cleansing.

Abrasives consist of finely divided particles of fused aluminum or plastic together with cleansing and wetting agents. Abrasives peel and remove surface debris and may assist resorption of papules and pustules. Despite vigorous rubbing, removal of comedones is not accomplished. Particles containing active agents, such as sodium tetraborate decahydrate, dissolve on use, and their abrasiveness is therefore limited.[163] The effectiveness of an abrasive cleanser with and without polyethylene granules showed no difference in results in patients with mild-to-moderate acne. These products are not indicated in most cases but may be used in a patient who responds empirically.[164]

EVALUATION OF THERAPEUTIC OUTCOMES

10 Provide a monitoring framework for patients with acne. Parameters should be monitored by the patient and recorded in a diary. Therapy should be appropriately tapered in response to improvement or resolution. The healthcare professional should be responsible for ensuring that the treatment plan remains on schedule and is effective with no adverse effects. The patient should be contacted within 2 to 3 weeks to determine progress.

Acne is poorly understood by adolescents. These patients often lack knowledge of the cause of the disorder and aggravating factors, indications for self-care versus prescription treatment, expected onset of effect, sequence of the healing process, duration of treatment, appropriate application of topical agents, maximal achievable effects, expected adverse effects, safety concerns, and the benefit to QOL. Clinicians should review patient understanding of each of these important factors to ensure patient adherence. There is often a need to supplement counseling sessions with written materials to which the patient can refer at home.

Good adherence is the key to treatment success. Other strategies to increase adherence include use of once-daily regimens, online follow-up visits, and remote digital imaging for ongoing lesion assessment.[165,166] A randomized controlled trial compared the effectiveness of automated online counseling to standard web-based education on improving acne knowledge. While both models had a significant increase in knowledge from baseline, after 12 weeks, mean improvement in knowledge was higher in the automated counseling group than in the standard Website group. The automated counseling Website group rated their educational material more useful and more enjoyable to view than did the standard Website group. Internet-based patient education appears to be an effective method of improving acne knowledge among adolescents.[167]

Monitoring of the Pharmaceutical Care Plan

Tables 117-2 to 117-4 provide a guide for monitoring patients with acne. Table 117-2 outlines individual drugs, their most common adverse effects, parameters to monitor, and issues to note. Table 117-3 outlines general effectiveness and safety end points, monitoring parameters, and degree of change and time frames for short- and long-term outcomes. Table 117-4 is a guide for monitoring acne patients with consideration to the severity grading of acne types I through IV.

TABLE 117-3

Monitoring Therapy for Acne: Parameters and Frequency

Person Responsible and Frequencies for Monitoring:		
Patient: daily while on drug therapy; Pharmacist: every 4-8 weeks of therapy or next pharmacy visit		
Parameter	**Time Frame/Degree of Change**	**Actions**
Short-Term Effectiveness End Points (Acne Resolution/Control)		
Lesion count	Decrease by 10%-25% within 4-8 weeks, with control, or more than a 50% decrease within 2-4 months	If end points are not achieved, refer to a physician for further therapy
Comedones	Resolve by 3-4 months	
Inflammatory lesions	Resolve within a few weeks	
Anxiety, depression	Achieve control or improvement within 2-4 months	
Long-Term Effectiveness End Points (Acne Resolution/Control)		
Progression of severity	No progression of severity	If end points are not achieved, refer to a physician for further therapy
Recurrent episodes	Lengthening of acne-free periods throughout therapy	
Scarring or pigmentation	No further scarring or pigmentation throughout therapy	
Safety End Points (Treatment Side Effects)		
Dermatitis, increased dryness, gastrointestinal upset, photosensitivity	No adverse effects	Refer to a physician for alternate therapy, dose reduction, discontinuation or additive palliative treatment, or preventative measures for adverse effects

TABLE 117-4

Monitoring Care Plans for Acne Types I Through IV

Acne Type	Description	Suggested Options	Follow-up Action If Patient Responds	Follow-up Action If Patient Does Not Respond in 3 Months	Adjustment in Therapy If Patient Does Not Respond Adequately to Previous Action
Type I	Mainly comedones with an occasional small inflamed papule or pustule; no scarring present	Topical retinoid or a fixed combination with a retinoid is the drug of choice; can also consider benzoyl peroxide or azelaic acid or salicylic acid	Continue until lesions are completely cleared and then stop or taper therapy	Treat as Type II acne	
Type II	Comedones and more numerous papules and pustules (mainly facial); mild scarring	Fixed-dose combination (adapalene and benzoyl peroxide) or benzoyl peroxide or topical retinoid or azelaic acid; if more severe, fixed-dose combination is preferred, with or without hormonal therapy and/or antibiotic, particularly if the trunk is involved	Continue until lesions are completely cleared and then stop or taper therapy	Treat as Type III acne	
Type III	Numerous comedones, papules and pustules, spreading to the back, chest, and shoulders, with an occasional cyst or nodule; moderate scarring	Fixed-dose combination with an oral antibiotic is preferred; oral isotretinoin or oral hormonal therapy can also be added	Oral antibiotics typically are prescribed for daily use over 4-6 months, with subsequent tapering and discontinuation as acne improves. Other agents can also be stopped or tapered now	Add oral contraceptive or antiandrogen (women only)	Oral isotretinoin (except in women who are or who may become pregnant); consider safety end points (potential adverse effects) before initiating therapy
Type IV	Numerous large cysts on the face, neck, and upper trunk; severe scarring	For males, monotherapy with oral isotretinoin or a retinoid fixed combination or oral antibiotics; for females, oral isotretinoin plus antiandrogenic hormonal therapy is preferred, or a fixed combination retinoid with oral antibiotics (consider high dose) and/or oral antiandrogenic hormonal therapy	Oral antibiotics typically are prescribed for daily use over 4-6 months, with subsequent tapering and discontinuation as acne improves Other agents can also be stopped or tapered now	If no response after 3-6 months, oral isotretinoin (except in women who are or who may become pregnant). Consider safety end points (potential adverse effects) before initiating therapy	

CONCLUSION

Considerable gaps remain in the understanding of acne, despite all that is known about the pathogenesis of acne and the mechanisms of effective drugs for controlling its symptoms, progression, and complications at structural, biochemical, and physiologic levels. It is still not possible to precisely define the cause of one of the most common skin diseases, nor is it possible to identify a cure for a condition that affects a very large proportion of the global population.

ABBREVIATIONS

BGA	best guideline acne
CAM	complementary and alternative medicine
COC	combination oral contraceptive
CRH	corticotropin-releasing hormone
FDA	Food and Drug Administration
GHQ	general health quality
HGL	high glycemic load
IGF	insulin-like growth factor
MMPP	mild-to-moderate papulopustular
P. acnes	*Propionibacterium acnes*
PAPA	pyogenic arthritis, pyoderma gangrenosum, acne
PBV	pollen bee venom
PDT	photodynamic therapy
QOL	quality of life
SAPHO	synovitis, acne, pustulosis, hyperostosis, osteitis syndrome
SPF	sun protection factor
TTO	time trade-off

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SELF-ASSESSMENT QUESTIONS

1. What is the **most accurate** statement regarding the epidemiology of acne vulgaris?

   A. Males present with an earlier onset in puberty.

   B. Females present with more severe signs and symptoms in puberty.

   C. Males have more severe symptoms in adulthood.

   D. There are no gender differences in acne prevalence.

2. What is the **most accurate** statement regarding the etiology of acne vulgaris?

   A. Acne is generally worse in the summer due to aggravation by ultraviolet light.

   B. Aggravation of acne through stress is a myth.

   C. Dietary influences may affect the expression of acne.

   D. Acne is not more serious if there is a hereditary link.

3. Select the **most important** of four pathophysiologic mechanisms underlying acne vulgaris:

   A. Increased follicular keratinization forming a microcomedone

   B. Increased production of sebum

   C. Bacterial lipolysis of sebum triglycerides to free fatty acids

   D. Inflammation

4. What is the **most accurate** statement regarding the clinical presentation of acne vulgaris?

   A. The open comedone is the first clinically visible lesion of acne.

   B. A pustule is usually greater than 5 mm in diameter.

   C. Nodules usually resolve within a few days without scarring.

   D. The open comedone is very stable and may persist for a long time.

5. Which of the following factors is the *least* important factor in the *differential diagnosis* of acne vulgaris?

   A. Betamethasone therapy

   B. Lithium therapy

   C. Polycystic ovary syndrome

   D. Vitamin B_{12} deficiency

6. Which of the following **can be excluded** as a basic goal of treatment of acne vulgaris?

   A. Reversing progression of signs and symptoms

   B. Limiting acne duration and recurrence

   C. Prevention of long-term disfigurement associated with scarring and hyperpigmentation

   D. Avoidance of psychological suffering

7. Which fact is **the least accurate** about comedone extraction?

   A. Fewer than 10% of comedone extractions are a complete success.

   B. Comedones may recur between 25 and 50 days following expression.

   C. Has been widely tested in clinical trials

D. Results in immediate cosmetic improvement

8. To prevent cosmetic acne, patients should:

A. Avoid self-care and use cosmetics applied during a beauty salon facial

B. Select “noncomedogenic” products

C. Select water-based products

D. Avoid hairspray

9. For mild-to-moderate acne with predominantly noninflammatory lesions (comedones), active agents of first choice include:

A. Retinoic acid, topical antibiotics, or benzoyl peroxide

B. Retinoic acid, topical or oral antibiotics, or benzoyl peroxide

C. Topical retinoids (eg, adapalene) or a fixed combination with a retinoid (eg, adapalene plus benzoyl peroxide)

D. Retinoic acid, salicylic acid, or benzoyl peroxide

10. For severe acne with inflammatory lesions (papules, pustules), moderate nodules, and cysts, the most appropriate drug regimens should include:

A. Tretinoin, adapalene, or tazrotene

B. The fixed-dose combination (adapalene plus benzoyl peroxide) with isotretinoin

C. Isotretinoin or topical or oral antibiotics

D. The fixed-dose combination (adapalene plus benzoyl peroxide) with an oral antibiotic

11. Treatment of mild scarring has best results with:

A. Dermabrasion or collagen implants

B. Chemical peels (eg, 70% glycolic acid)

C. Laser therapy

D. Nonprescription alpha-hydroxy acids

12. Comparisons of salicylic acid and benzoyl peroxide have shown:

A. Salicylic acid to be equal or slightly inferior to benzoyl peroxide in reducing number of inflammatory lesions

B. The two products have similar efficacy

C. Benzoyl peroxide could be superior in acting against later steps

D. The effect of different bases is not relevant

13. As a group, the topical retinoids are:

A. Useful in the management of both comedonal and inflammatory acne

B. Ranked in order of peeling efficacy as tretinoin < adapalene < tazarotene

C. Decrease production of sebum and are thus useful for severe acne

D. Are contraindicated in cases of postinflammatory hyperpigmentation

14. Acne patients who wish to increase ultraviolet light exposure to improve acne should use the following therapies with caution:

A. Minocycline and benzoyl peroxide

B. Doxycycline and retinoic acid

C. Retinoic acid and benzoyl peroxide

D. Topical clindamycin and minocycline

15. Choose the **most correct** statement:

A. Azeleic acid therapy should include monitoring for hyperpigmentation.

B. Patients on isotretinoin therapy should be monitored for signs of depression.

C. Control of acne is reflected in a reduction of lesion counts by 50% decrease within 2-4 weeks.

D. Comedones should resolve within a few weeks.

16. Kate presents at a pharmacy with her 3-month-old son Aiden. Aiden has scattered red papules and two to three pustules on both cheeks. There are no blisters or scales. He is not on any medications. He seems fine, he is eating well, and he isn't irritable or fussy. Which of the following is the **most appropriate** recommendation?

A. Hydrocortisone 0.5% cream

B. Benzoyl peroxide 5% lotion

C. An emollient

D. No treatment necessary

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** See section "Epidemiology" of the Acne Vulgaris this chapter.
2. **C.** See subsection "Dietary Influences" of the Acne Vulgaris this chapter.
3. **A.** See section "Pathophysiology" of the Acne Vulgaris this chapter.
4. **D.** See box "Clinical Presentation" in the Acne Vulgaris this chapter.
5. **D.** See subsection "Differential Diagnosis" of the Acne Vulgaris this chapter.
6. **A.** Progression of acne cannot be reversed.
7. **C.** As noted in subsection "Comedone Extraction" of the Acne Vulgaris this chapter, this intervention has not been widely tested.
8. **D.** See subsection "Prevention of Cosmetic Acne" of the Acne Vulgaris this chapter.
9. **C.** See subsection "Managing Acne" of the Acne Vulgaris this chapter.
10. **D.** See subsection "Managing Acne" of the Acne Vulgaris this chapter.
11. **D.** See subsection "Treatment of Scarring" of the Acne Vulgaris this chapter.

12. **B.** See subsections on Salicylic Acid and Benzoyl Peroxide" of the Acne Vulgaris chapter.

13. **A.** See subsection "Topical Retinoids" of the Acne Vulgaris this chapter.

14. **B.** Both agents are photosensitizers.

15. **B.** See subsection "Issues Regarding Responsible and Informed Use" of the Acne Vulgaris this chapter.

16. **D.** Condition is self-limiting and no treatment is needed.