Guidelines of care for the management of acne vulgaris

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Acne is one of the most common disorders treated by dermatologists and other health care providers. While it most often affects adolescents, it is not uncommon in adults and can also be seen in children. This evidence-based guideline addresses important clinical questions that arise in its management. Issues from grading of acne to the topical and systemic management of the disease are reviewed. Suggestions on use are provided based on available evidence. (J Am Acad Dermatol 2016;74:945-73.)

Key words: acne; acne management; acne vulgaris; amoxicillin; antiandrogens; azithromycin; benzoyl peroxide; clindamycin; contraceptive agents; diet and acne; doxycycline; erythromycin; grading and classification of acne; guidelines; hormonal therapy; isotretinoin; light therapies; microbiological and endocrine testing; oral corticosteroids; *Propionibacterium acnes*; retinoids; salicylic; spironolactone; systemic therapies; tetracyclines; topical antibiotics; trimethoprim.

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care, or be deemed inclusive of all proper methods of care, nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy or technique must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

SCOPE

This guideline addresses the management of adolescent and adult patients who present with acne vulgaris (AV). This document will discuss various acne treatments, including topical therapies, systemic agents, and physical modalities, including

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Table I. Clinical questions used to structure the evidence review

What systems are most commonly used for the grading and classification of adult acne and acne vulgaris in adolescents (11-21 years of age) to adults?

What is the role of microbiologic and endocrine testing in evaluating patients with adult acne and acne vulgaris in adolescents to adults?

What is the effectiveness and what are the potential side effects of topical agents in the treatment of adult acne and acne vulgaris in adolescents to adults, including:
- Retinoids and retinoid-like drugs
- Benzoyl peroxide
- Topical antibiotics
- Salicylic/azelaic acids
- Sulfur and resorcinol
- Aluminum chloride
- Zinc
- Combinations of topical agents

What is the effectiveness and what are the potential side effects of the following systemic antibacterial agents in the treatment of adult acne and acne vulgaris in adolescents to adults, including:
- Tetracyclines: doxycycline and minocycline
- Macrolides: erythromycin and azithromycin
- Clindamycin
- Trimethoprim (with or without sulfamethoxazole)
- Ampicillin/amoxicillin

What is the effectiveness and what are the potential side effects of hormonal agents in the treatment of adult acne and acne vulgaris in adolescents to adults, including:
- Contraceptive agents
- Spironolactone
- Antiandrogens
- Oral corticosteroids

What is the effectiveness and what are the potential side effects of isotretinoin in the treatment of adult acne and acne vulgaris in adolescents to adults?

What is the effectiveness and potential side effects of physical modalities for the treatment of acne vulgaris in adolescents to adults, including:
- Intralesional steroids
- Chemical peels
- Comedo removal
- Lasers and photodynamic therapy*

What is the effectiveness and what are the potential side effects of complementary/alternative therapies in the treatment of adult acne and acne vulgaris in adolescents to adults, including:
- Herbal agents
- Homeopathy
- Psychological approaches
- Massage therapy
- Hypnosis/biofeedback

What is the role of diet in adult acne in adolescents to adults?

*Indicates a new clinical question for this guideline.

lasers and photodynamic therapy. In addition, grading/classification system, microbiology and endocrinology testing, complementary/alternative therapies, and the role of diet will be reviewed. This guideline does not examine the treatment of acne sequelae (eg, scarring or postinflammatory dyschromia).

METHODS

A work group of 17 recognized acne experts, 1 general practitioner, 1 pediatrician, and 1 patient was convened to determine the scope of the guideline and identify clinical questions (Table I) in the diagnosis and management of AV. Work group members completed a disclosure of interests, which

was periodically updated and reviewed throughout guideline development. If a potential conflict was noted, the work group member recused him or herself from discussion and drafting of recommendations pertinent to the topic area of the disclosed interest.

An evidence-based model was used and evidence was obtained for the clinical questions (Table I) using a systematic search of PubMed and the Cochrane Library database from May 2006 through September 2014 for clinical questions addressed in the previous version of this guideline published in 2007, and 1964 to 2014 for all newly identified clinical questions. Searches were prospectively limited to publications in the English language. MeSH terms and strings used in various combinations in the literature search included: acne or acne vulgaris combined with treatment, therapy, prevention, prophylaxis, grading, classification, scoring, microbiology, endocrinology, hormone, topical, retinoid, benzoyl peroxide (BP), antibiotic, doxycycline, minocycline, tetracycline, macrolide, erythromycin, azithromycin, trimethoprim (with or without sulfamethoxazole), oral contraceptives, antiandrogen, corticosteroid, isotretinoin, peel, complementary, alternative, herbal, diet, glycemic index, milk, antioxidants, probiotics, and fish oil. Additional studies were identified by hand-searching bibliographies of publications, including reviews and metaanalyses.

A total of 1145 abstracts were initially assessed for possible inclusion; 242 were retained for final review based on relevancy and the highest level of available evidence for the outlined clinical questions. Evidence tables were generated for these studies and used by the work group in developing recommendations. In addition, the evidence tables generated for the Academy's previous acne guideline were also used by the work group. The Academy's previous published guidelines on acne were also evaluated, as were other current published guidelines on acne.[1,2] Relevant references published after September 2014 are provided solely as supplemental supporting text information for recommendations as derived from the systematic search, and to address comments received during the guideline review and approval process.

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy (SORT) developed by editors of the US family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*).[3] Evidence was graded using a 3-point scale based on the quality of methodology (eg, randomized control trial, case control, prospective/retrospective cohort, case series, etc) and the overall focus of the study (ie, diagnosis, treatment/prevention/screening, or prognosis) as follows:

I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life).
II. Limited-quality patient-oriented evidence.
III. Other evidence, including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed on the best available evidence tabled in the guideline. The strength of recommendation was ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence.
B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

In those situations where documented evidence-based data were not available or were showing inconsistent or limited conclusions, expert opinion and medical consensus was used to generate clinical recommendations.

This guideline has been developed in accordance with the American Academy of Dermatology/American Academy of Dermatology Association "Administrative Regulations for Evidence-Based Clinical Practice Guidelines" (version approved August 2012), which include the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.[4] This guideline will be considered current for a period of 5 years from the date of publication, unless reaffirmed, updated, or retired at or before that time.

DEFINITION

AV is a chronic inflammatory dermatosis notable for open or closed comedones (blackheads and whiteheads) and inflammatory lesions, including papules, pustules, or nodules (also known as cysts).

INTRODUCTION

Acne is a common skin disease, especially in adolescents and young adults. Approximately 50 million people in the United States have AV.[5] Acne

	Mild	Moderate	Severe
1st Line Treatment	Benzoyl Peroxide (BP) or Topical Retinoid -or- Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic	Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Antibiotic + Topical Retinoid + BP -or- Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic	Oral Antibiotic + Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Isotretinoin
Alternative Treatment	Add Topical Retinoid or BP (if not on already) -or- Consider Alternate Retinoid -or- Consider Topical Dapsone	Consider Alternate Combination Therapy -or- Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin	Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin

Fig 1. Treatment algorithm for the management of acne vulgaris in adolescents and young adults. The *double asterisks* (**) indicate that the drug may be prescribed as a fixed combination product or as separate component. *BP*, Benzoyl peroxide.

Table II. Recommendations for grading and classification of acne

Clinicians may find it helpful to use a consistent grading/classification scale (encompassing the numbers and types of acne lesions as well as disease severity, anatomic sites, and scarring) to facilitate therapeutic decisions and assess response to treatment.
Currently, no universal acne grading/classifying system can be recommended.

affects approximately 85% of teenagers, but can occur in most age groups[6] and can persist into adulthood. The prevalence of acne in adult women is about 12%.[7] There is no mortality associated with acne, but there is often significant physical and psychological morbidity, such as permanent scarring, poor self-image, depression, and anxiety. The direct cost of the disease is estimated to exceed $3 billion per year.[6]

Acne is a multifactorial inflammatory disease affecting the pilosebaceous follicles of the skin. The current understanding of acne pathogenesis is continuously evolving. Key pathogenic factors that play an important role in the development of acne are follicular hyperkeratinization, microbial colonization with *Propionibacterium acnes*, sebum production, and complex inflammatory mechanisms involving

Table III. Strength of recommendations for the management and treatment of acne vulgaris

Recommendation	Strength of recommendation	Level of evidence	References
Grading/classification system	B	II, III	8-39
Microbiologic testing	B	II, III	40-48
Endocrinologic testing	B	I, II	49-56
Topical therapies			
Benzoyl peroxide	A	I, II	57-59
Topical antibiotics (eg, clindamycin and erythromycin)	A	I, II	60-66
Combination of topical antibiotics and benzoyl peroxide	A	I	67-69
Topical retinoids (eg, tretinoin, adapalene, and tazarotene)	A	I, II	70-81
Combination of topical retinoids and benzoyl peroxide/topical antibiotic	A	I, II	75,76
Azelaic acid	A	I	82,83
Dapsone	A	I, II	84-86
Salicylic acid	B	II	87
Systemic antibiotics			
Tetracyclines (eg, tetracycline, doxycycline, and minocycline)	A	I, II	88-91
Macrolides (eg, azithromycin and erythromycin)	A	I	92
Trimethoprim (with or without sulfamethoxazole)	B	II	93,94
Limiting treatment duration and concomitant/maintenance topical therapy	A	I, II	95-97
Hormonal agents			
Combined oral contraceptives	A	I	98-101
Spironolactone	B	II, III	102,103
Flutamide	C	III	104,105
Oral corticosteroids	B	II	106
Isotretinoin			
Conventional dosing	A	I, II	107-133
Low-dose treatment for moderate acne	A	I, II	134-138
Monitoring	B	II	139-142
iPLEDGE and contraception	A	II	143,144
Miscellaneous therapies and physical modalities			
Chemical peels	B	II, III	145-147
Intralesional steroids	C	III	148,149
Complementary and alternative therapies (eg, tea tree oil, herbal, and biofeedback)	B	II	150-156
Role of diet in acne			
Effect of glycemic index	B	II	157-161
Dairy consumption	B	II	162-164

both innate and acquired immunity. In addition, studies have suggested that neuroendocrine regulatory mechanisms, diet, and genetic and nongenetic factors all may contribute to the multifactorial process of acne pathogenesis. An algorithm for the treatment and management of acne in adolescents and young adults is shown in Fig 1.

SYSTEMS FOR THE GRADING AND CLASSIFICATION OF ACNE

Acne grading systems may be useful in patient care. Such systems can assist in more specific classification of disease, help determine appropriate treatment options, and monitor improvement during the treatment course. Recommendations for grading and classifying acne are shown in Table II, and the strength of recommendations for grading and classifying acne is shown in Table III.

Numerous acne assessment tools have been described, taking into account various factors, such as type of acne, severity of acne, number of acne lesions, anatomic location/extent of acne,[8] quality of life and other psychosocial metrics,[9-13] and scarring,[14] among other measures.[15-24] Recently, 18 of these grading scales were ranked based on a variety of characteristics.[25] To date, there is no universally agreed-upon grading system, and systems can differ greatly between studies. In addition, interobserver reliability of these scales varies, but has been poor in some studies.[17,26,27] Methods such as photographic standards have been used to improve reproducibility.

Improvements in digital technology, photographic equipment, and teledermatology may allow for accurate, remote assessment of acne in the near future.[28-30] Scientific measures, such as ultraviolet-

Table IV. Recommendations for microbiologic and endocrinologic testing

Routine microbiologic testing is not recommended in the evaluation and management of patients with acne
Those who exhibit acne-like lesions suggestive of Gram-negative folliculitis may benefit from microbiologic testing
Routine endocrinologic evaluation (eg, for androgen excess) is not recommended for the majority of patients with acne
Laboratory evaluation is recommended for patients who have acne and additional signs of androgen excess

induced red fluorescence,[31-33] casual sebum level,[34,35] skin capacitance imaging,[36] skin surface pH,[37,38] and transepidermal water loss[39] may also help to more objectively classify and rate acne in the future. Reproducibility, as well as ease of use and acceptance by dermatologists, will be essential for the success of any grading system.

MICROBIOLOGIC TESTING

P acnes, a Gram-positive anaerobic rod, is the primary bacterium implicated in acne.[40-42] It has specific, nonstandard culture requirements that prohibit routine culture. Currently, microbiologic testing of acne lesions is largely unnecessary because it does not affect management, and successful antibiotic treatment may not result from a reduction of bacterial numbers.[40] The antibiotics typically used in the management of acne, tetracyclines, have additional antiinflammatory actions independent of microbial killing. As additional information is learned about *P acnes* from a molecular and genetic perspective, and its role in inciting inflammation in acne,[43-48] more targeted therapeutic interventions in the future may result. Recommendations for microbiologic testing of acne are shown in Table IV and the strength of recommendations for microbiologic testing is shown in Table III.

The prime situation where microbiologic testing is useful in patients with acne is in evaluating for Gram-negative folliculitis. This uncommon disorder presents as uniform and eruptive pustules, with rare nodules, in the perioral and perinasal regions, typically in the setting of prolonged tetracycline use. It is caused by various bacteria, such as Klebsiella and Serratia, and is unresponsive to many conventional acne treatments. Gram-negative folliculitis is typically diagnosed via culture of the lesions, and is generally treated with isotretinoin or an antibiotic to which the bacteria are sensitive. In cases of acne unresponsive to typical treatments—particularly with prominent truncal involvement or monomorphic appearance—pityrosporum folliculitis should be considered. *Staphylococcus aureus* cutaneous infections may appear similar to acne, and should be considered in the differential, particularly in cases of acute eruptions; a swab culture may be helpful in these cases.

ENDOCRINOLOGIC TESTING

While the role of androgens in acne pathogenesis is well known, endocrinologic evaluation is only warranted in certain cases, because most acne patients will have normal hormone levels. Testing is primarily indicated for patients with clinical features or a history of hyperandrogenism. In prepubertal children, these features include: acne, early-onset body odor, axillary or pubic hair, accelerated growth, advanced bone age, and genital maturation. Growth charts and a hand film for bone age are good screening tools before specific hormonal testing.[1,49] In postpubertal females, clinical signs, such as infrequent menses, hirsutism, androgenetic alopecia, infertility, polycystic ovaries, clitoromegaly, and truncal obesity warrant further hormonal testing.[1,2,50-52,165] Recalcitrant acne caused by androgen excess can also be seen in both men and women with nonclassical congenital adrenal hyperplasia (eg, 21-hydroxylase deficiency).[166,167] Recommendations for endocrinologic testing of acne are shown in Table IV, and the strength of recommendations for endocrinologic testing is shown in Table III.

The most common cause of elevated androgens of ovarian origin is polycystic ovarian syndrome (PCOS).[53] It has recently been proposed that diagnosis of PCOS in adult females requires 2 of the 3 following criteria: androgen excess (clinical or biochemical), ovulatory dysfunction (oligo- or anovulation), or polycystic ovaries (based on ultrasonographic findings). In adolescent females, the diagnosis of PCOS can be made based on hyperandrogenism (clinical or biochemical) in the presence of persistent oligomenorrhea.[168] The differential diagnosis of PCOS includes thyroid disease, prolactin excess, and nonclassical congenital adrenal hyperplasia, among others.[168]

Hormonal testing and interpretation of testing is complex. A typical hormone-screening panel includes free and total testosterone, dehydroepiandrosterone sulfate (DHEA-S), androstenedione, luteinizing hormone, and follicle-stimulating hormone.[49,51-54,165] Growth hormone, insulin-like

Table V. Recommendations for topical therapies

Benzoyl peroxide or combinations with erythromycin or clindamycin are effective acne treatments and are recommended as monotherapy for mild acne, or in conjunction with a topical retinoid, or systemic antibiotic therapy for moderate to severe acne
Benzoyl peroxide is effective in the prevention of bacterial resistance and is recommended for patients on topical or systemic antibiotic therapy
Topical antibiotics (eg, erythromycin and clindamycin) are effective acne treatments, but are not recommended as monotherapy because of the risk of bacterial resistance
Topical retinoids are important in addressing the development and maintenance of acne and are recommended as monotherapy in primarily comedonal acne, or in combination with topical or oral antimicrobials in patients with mixed or primarily inflammatory acne lesions
Using multiple topical agents that affect different aspects of acne pathogenesis can be useful. Combination therapy should be used in the majority of patients with acne
Topical adapalene, tretinoin, and benzoyl peroxide can be safely used in the management of preadolescent acne in children
Azelaic acid is a useful adjunctive acne treatment and is recommended in the treatment of postinflammatory dyspigmentation
Topical dapsone 5% gel is recommended for inflammatory acne, particularly in adult females with acne
There is limited evidence to support recommendations for sulfur, nicotinamide, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc in the treatment of acne

growth factor, lipid levels, insulin, sex hormone–binding globulin, free 17-β-hydroxysteroids, free androgen index, prolactin, estrogen, and progesterone may also be abnormal in those with severe acne.[52,54-56,165,169] Insulin resistance may also represent a risk factor for acne in certain patients.[170] Patients with abnormal test results, or in whom there is a persistent concern for a hormonal disorder, should be further evaluated by an endocrinologist.

TOPICAL THERAPIES

The topical therapy of AV includes the usage of agents that are available over the counter or via prescription. Therapy choice may 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. Recommendations for use of topical therapies are shown in Table V, and the strength of recommendations for treatment of acne with topical therapies is shown in Table III. Prescribing information for all topical therapies is located in Supplementary Tables I-XIII.(Please note all Supplemental Tables can be found at www.jaad.org.)

Commonly used topical acne therapies include BP, salicylic acid, antibiotics, combination antibiotics with BP, retinoids, retinoid with BP, retinoid with antibiotic, azelaic acid, and sulfone agents. Although most physicians have anecdotal regimens they find beneficial, agents reviewed here are limited to those approved by the US Food and Drug Administration (FDA) for use in the United States, and for which peer-reviewed literature has been published.

BP is an antibacterial agent that kills *P acnes* through the release of free oxygen radicals and is also mildly comedolytic.[171,172] No resistance to this agent has been reported, and the addition of BP to regimens of antibiotic therapy enhances results and may reduce resistance development. BP is available as topical washes, foams, creams, or gels, and can used as leave-on or wash-off agents. Strengths available for acne therapy range from 2.5% to 10%. BP therapy is limited by concentration-dependent irritation, staining and bleaching of fabric, and uncommon contact allergy. Total skin contact time and formulation can also affect efficacy. Lower concentrations (eg, 2.5-5%), water-based, and wash-off agents may be better tolerated in patients with more sensitive skin.[57,58] Results can be noted in as soon as 5 days.[59]

Topical antibiotics for acne accumulate in the follicle and have been postulated to work through antiinflammatory mechanisms and via antibacterial effects.[60] These agents are best used in combination with BP (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. Clindamycin 1% solution or gel is currently the preferred topical antibiotic for acne therapy.[173] Topical erythromycin in 2% concentration is available as a cream, gel, lotion, or pledget,[61,62] but has reduced efficacy in comparison with clindamycin because of resistance of cutaneous

Staphylococci and *P acnes*.[60,63-66] Stable, fixed-combination agents are available with erythromycin 3%/BP 5%, clindamycin 1%/BP 5%, and clindamycin 1%/BP 3.75%.[67-69,174] Combination agents may enhance compliance with treatment regimens. Rare reports of diarrhea or *Clostridium difficile*–related colitis with clindamycin topically have appeared in the literature, but the risk appears low.[66] Tolerance of these agents is excellent; clindamycin alone is pregnancy category B.

Topical retinoids are vitamin A derivatives that are prescription agents with randomized, double-blind, placebo-controlled trials supporting their use for acne treatment.[70-72,175] Three active agents are available: tretinoin (0.025-0.1% in cream, gel, or microsphere gel vehicles), adapalene (0.1%, 0.3% cream, or 0.1% lotion[73,74]), and tazarotene (0.05%, 0.1% cream, gel or foam). Each retinoid binds to a different set of retinoic acid receptors: tretinoin to alpha, beta, and gamma, and tazarotene and adapalene, selectively, to beta and gamma—thereby conferring slight differences in activity, tolerability, and efficacy. Retinoids are the core of topical therapy for acne because they are comedolytic, resolve the precursor microcomedone lesion, and are antiinflammatory.

These agents enhance any topical acne regimen and allow for maintenance of clearance after discontinuation of oral therapy. Retinoids are ideal for comedonal acne and, when used in combination with other agents, for all acne variants. Three topical agents are available that contain retinoids in combination with other products: adapalene 0.1%/BP 2.5%, approved for use in patients ≥9 years of age, and 2 agents with fixed combination clindamycin phosphate 1.2%/tretinoin 0.025% gel, approved for patients ≥12 years of age.[75,76,176]

Retinoid use may be limited by side effects, including dryness, peeling, erythema, and irritation, which can be mitigated by reduced frequency of application.[177] Given any single agent, higher concentrations may be more efficacious, but with greater side effects.[70,74,77] Some formulations of tretinoin (primarily generic products) are not photostable and should be applied in the evening. Tretinoin also may be oxidized and inactivated by the coadministration of BP. It is recommended that the 2 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.

There are several head-to-head studies with retinoid products. Some support greater efficacy of tazarotene over adapalene and tretinoin, and adapalene over tretinoin, but the concentrations and formulations used were varied.[73,78-80] Data suggest that adapalene is better tolerated than multiple concentrations of tretinoin, but this is based on older formulations.[81] Overall, the limitations of the existing studies prohibit direct efficacy comparisons of topical retinoids.

Tretinoin and adapalene are pregnancy category C, while tazarotene is category X; therefore, patients should be counseled on these pregnancy risks when starting a retinoid or if a woman patient desires pregnancy.

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

Azelaic acid 20% is mildly effective as a comedolytic, antibacterial, and antiinflammatory agent. The agent has use in patients with sensitive skin or of Fitzpatrick skin types IV or greater because of the lightening effect of the product on dyspigmentation.[82,83,178] Azelaic acid is category B in pregnancy.

The sulfone agent, dapsone 5% gel, is available as a twice-daily agent for the therapy of AV. In clinical trials, topical dapsone showed modest to moderate efficacy, primarily in the reduction of inflammatory lesions.[84,85] Combination with topical retinoids may be indicated if comedonal components are present. The mechanism of action is poorly understood, and its ability to kill *P acnes* has been poorly studied. It is generally thought to work as an antiinflammatory agent. The benefit in women seems to exceed the benefit in male and adolescent patients.[86,179] Topical dapsone may be oxidized by the coapplication of BP, causing orange-brown coloration of the skin which can be brushed or washed off. Topical dapsone 5% gel is pregnancy category C and has efficacy and safety data down to patients 12 years of age. Glucose-6-phosphate dehydrogenase testing is not required before starting topical dapsone.

Salicylic acid is a comedolytic agent that is available over the counter in 0.5% to 2% strengths for the therapy of AV. Both wash-off and leave-on preparations are well tolerated. Clinical trials demonstrating the efficacy of salicylic acid in acne are limited.[87,180]

Although sulfur and resorcinol have been used for many years in the treatment of acne, evidence from

Table VI. Recommendations for systemic antibiotics

Systemic antibiotics are recommended in the management of moderate and severe acne and forms of inflammatory acne that are resistant to topical treatments
Doxycycline and minocycline are more effective than tetracycline, but neither is superior to each other
Although oral erythromycin and azithromycin can be effective in treating acne, its use should be limited to those who cannot use the tetracyclines (ie, pregnant women or children <8 years of age). Erythromycin use should be restricted because of its increased risk of bacterial resistance
Use of systemic antibiotics, other than the tetracyclines and macrolides, is discouraged because there are limited data for their use in acne. Trimethoprim-sulfamethoxazole and trimethoprim use should be restricted to patients who are unable to tolerate tetracyclines or in treatment-resistant patients
Systemic antibiotic use should be limited to the shortest possible duration. Re-evaluate at 3-4 months to minimize the development of bacterial resistance. Monotherapy with systemic antibiotics is not recommended
Concomitant topical therapy with benzoyl peroxide or a retinoid should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy

peer-reviewed literature supporting their efficacy is lacking.[181] Aluminum chloride possesses antibacterial activity and, therefore, has been investigated in the treatment acne. Of 2 peer-reviewed studies, 1 found benefit[182] and 1 did not.[183] Topical zinc alone is ineffective.[184-186] There is some evidence to suggest the efficacy of sodium sulfacetamide.[187-189] Topical niacinamide (nicotinomide) 2% to 4% gel is available over the counter. The limited studies available compare its efficacy to topical clindamycin 1% gel.[190,191]

SYSTEMIC ANTIBIOTICS

Systemic antibiotics have been a mainstay of acne treatment for years. They are indicated for use in moderate to severe inflammatory acne and should be used in combination with a topical retinoid and BP.[95,192,193] Evidence supports the efficacy of tetracycline, doxycycline, minocycline, trimethoprim/sulfamethoxazole (TMP/SMX), trimethoprim, erythromycin, azithromycin, amoxicillin, and cephalexin. Recommendations for systemic antibiotics are shown in Table VI, and the strength of recommendations for treatment of acne with systemic antibiotics is shown in Table III. Prescribing information for systemic antibiotics is located in the Supplementary Tables XIV-XXII.

The tetracycline class of antibiotics should be considered first-line therapy in moderate to severe acne, except when contraindicated because of other circumstances (ie, pregnancy, ≤8 years of age, or allergy). The antibiotics of the tetracycline class work by inhibiting protein synthesis by binding the 30S subunit of the bacterial ribosome. This class also has notable antiinflammatory effects, including inhibiting chemotaxis and metalloproteinase activity. Previous guidelines recommended minocycline as superior to doxycycline in reducing *P acnes*.[1] However, a recent Cochrane review of clinical trials found minocycline effective but not superior to other antibiotics in the treatment of acne.[88] There are few studies addressing dosing of the tetracycline class. Minocycline in an extended release form appears safest (at 1 mg/kg), but no dose response was found for efficacy.[194] Doxycycline appears effective in the 1.7 to 2.4 mg/kg dose range.[89] Subantimicrobial dosing of doxycycline (ie, 20 mg twice daily to 40 mg daily) has also shown efficacy in patients with moderate inflammatory acne.[195,196]

Erythromycin and azithromycin have also been used in the treatment of acne. The mechanism of action for the macrolide class of antibiotics is to bind the 50S subunit of the bacterial ribosome. Again, there are some antiinflammatory properties for these medications, but the mechanisms are not well understood. Azithromycin has been primarily studied in the treatment of acne in open label studies with different pulse dosing regimens ranging from 3 times a week to 4 days a month, with azithromycin being an effective treatment in the time span evaluated—usually 2 to 3 months.[92,197-204] A recent randomized controlled trial comparing 3 days per month of azithromycin to daily doxycycline did show superiority of doxycycline.[205] Macrolides as the penicillin class represent an alternative when traditional antibiotics cannot be used.

TMP/SMX and trimethoprim have also been used for the treatment of acne. Sulfamethoxazole is bacteriostatic by blocking bacterial synthesis of folic acid, which is necessary for cell division. Trimethoprim is a folic acid analog that inhibits the enzyme dihydrofolate reductase. The 2 agents work together to block nucleotide and amino acid synthesis in the bacteria. Outside of case reports, there is 1 small, double-blind study showing that TMP/SMX is as effective as oxytetracycline.[93]

Although data supporting their use are limited, penicillins and cephalosporins are sometimes used

Table VII. Recommendations for hormonal agents

Estrogen-containing combined oral contraceptives are effective and recommended in the treatment of inflammatory acne in females
Spironolactone is useful in the treatment of acne in select females
Oral corticosteroid therapy can be of temporary benefit in patients who have severe inflammatory acne while starting standard acne treatment
In patients who have well documented adrenal hyperandrogenism, low-dose oral corticosteroids are recommended in treatment of acne

in the treatment of acne and can be used as an alternative treatment when circumstances dictate. In particular, these medications represent a useful option in patients who may be pregnant or who have allergies to the other classes of antibiotics. These antibiotics work by binding the penicillin-binding proteins in the bacterial cell membrane and inhibiting bacterial cell wall synthesis. There are few references to support the use of these medications in the treatment of acne outside of case reports. However, there is a small retrospective chart review with cephalexin where the majority of patients showed some clinical improvement on this medication.[94]

Adverse events of systemic therapy are often a concern to patients and practitioners. However, severe adverse effects of systemic antibiotics in the treatment of acne are rare. Vaginal candidiasis and drug eruptions can occur with any antibiotic.

Adverse events with the tetracycline class vary with each medication. Photosensitivity can be seen with the tetracycline class, doxycycline being more photosensitizing than minocycline. Doxycycline is more frequently associated with gastrointestinal disturbances, and higher doses are more likely to cause symptoms.[89] Minocycline has been associated with tinnitus, dizziness, and pigment deposition of the skin, mucous membranes, and teeth. Minocycline pigmentation is more common in patients taking higher doses for longer periods of time. Doxycycline is primarily metabolized by the liver, and can be used safely in most patients with renal impairment. When minocycline is compared to other tetracyclines, more serious adverse events are reported (8.8 cases per 100,000 patient years).[88,90] The rare serious events associated with minocycline include autoimmune disorders, such as drug reaction with eosinophilia and systemic symptoms (DRESS), drug-induced lupus, and other hypersensitivity reactions.[91,206-209] Finally, pseudotumor cerebri is a rare phenomenon associated with the tetracycline class of antibiotics.

The adverse events of TMP/SMX include gastrointestinal upset, photosensitivity, and drug eruptions. Multiple cutaneous reactions have been observed with patients on this medication, the most severe eruptions being Stevens–Johnson syndrome and toxic epidermal necrolysis.[210,211] Such severe eruptions are more common in patients with HIV. The relative risk for such a severe reaction varies, but is still a rare event, with studies citing the crude relative risk at 172.[211] Disorders of the hematopoietic system can also occur with TMP/SMX and can include serious blood dyscrasias, such as neutropenia, agranulocytosis, aplastic anemia, and thrombocytopenia. Although these are rare adverse events, patients on long-term therapy with this medication should be periodically monitored with a complete blood cell count. Cases of fulminant hepatitis necrosis have also occurred in patients taking this medication, as has respiratory hypersensitivity. The concurrent use of TMP/SMX and methotrexate (MTX) can be associated with severe toxicity (Supplementary Table XVII).

The macrolide class of antibiotics is most commonly associated with gastrointestinal disturbances. Erythromycin is associated with a higher incidence of diarrhea, nausea, and abdominal discomfort than azithromycin. Macrolides have been reported to cause cardiac conduction abnormalities, and rarely hepatotoxicity has been reported. Macrolide antibiotics can also decrease metabolism of cyclosporine. Azithromycin has been associated with cutaneous hypersensitivity reactions.

Penicillins and cephalosporins are most associated with the adverse events of hypersensitivity reactions ranging from mild drug eruptions to anaphylaxis. Gastrointestinal disturbances are also common and include nausea, diarrhea, and abdominal distention and discomfort.

When prescribing systemic antibiotics, the issue of bacterial resistance remains a major concern. The Centers for Disease Control and Prevention (CDC) has stressed antibiotic stewardship. This is an initiative to promote the appropriate use of antibiotics where patients receive the right dose of the right antibiotic at the right time for the right duration. Limiting antibiotic use to the shortest possible duration, ideally 3-4 months, can be accomplished with the concomitant use of a retinoid

Table VIII. World Health Organization recommendations for combined oral contraceptive usage eligibility*

COC use not recommended	Caution or special monitoring
Pregnancy	Breastfeeding (6 weeks-6 months postpartum)
Current breast cancer	Postpartum (<21 days)
Breastfeeding <6 weeks postpartum	Age ≥35 years and light smoker (<15 cigarettes per day)
Age ≥35 years and heavy smoker (≥15 cigarettes per day)	History of hypertension (including pregnancy) or if monitoring is not feasible
Hypertension: systolic, ≥160 mm Hg; diastolic, ≥100 mm Hg	Hypertension: systolic, 140-159 mm Hg; diastolic, 90-99 mm Hg; or controlled and monitored
Diabetes with end-organ damage	Headaches: migraine without focal neurologic symptoms <35 years
Diabetes >20 years duration	Known hyperlipidemia should be assessed (eg, type and severity)
History of or current deep vein thrombosis or pulmonary embolism	History of breast cancer with ≥5 years of no disease
Major surgery with prolonged immobilization	Biliary tract disease
Ischemic heart disease (history or current); valvular heart disease with complications	Mild compensated cirrhosis
History of cerebrovascular accident	History of cholestasis related to COC use
Headaches (eg, migraine with focal neurologic symptoms at any age, or without aura if ≥35 years)	Concurrent use of drugs that affect liver enzymes
Active viral hepatitis	
Severe decompensated cirrhosis	
Liver tumor (benign or malignant)	

COC, Combined oral contraceptive.
*Data taken from Arrington et al.[219]

or retinoid/BP.[212,213] While limiting the use of systemic antibiotics is necessary, the work group's consensus agrees there are a subset of patients for whom alternative therapies are inappropriate and who may require a longer course of antibiotics even while taking topical medications. In such patients, consistent follow-up and reevaluation should be used to use the antibiotic for the shortest time necessary. Monotherapy with oral antibiotics is strongly discouraged. The use of topical maintenance regimens cannot be overemphasized. Topical therapies can accomplish continued efficacy months after the discontinuation of systemic antibiotics.[95,96,212,214] The work group's consensus agrees that such maintenance is paramount to reducing antibiotic resistance.[215] Other attempts to limit antibiotic use revolve around different dosing recommendations, such as pulse dosing and submicrobial dosing. No alternate dosing routines consistently appear superior to standard dosing.

Finally, limiting systemic antibiotic use is urged because of the reported associations of inflammatory bowel disease,[97] pharyngitis,[216] *C difficile* infection,[217,218] and the induction of Candida vulvovaginitis.

HORMONAL AGENTS

Combination oral contraceptive pills (COCs) contain both an estrogen and a progestin component. COCs were first approved by the FDA for contraception in the United States in 1960. They prevent ovulation and pregnancy by inhibiting gonadotropin-releasing hormone and, subsequently, follicle-stimulating and luteinizing hormones. These hormones are needed to begin follicular maturation and for ovulation; in their absence, ovulation does not occur. Recommendations for hormonal agents are shown in Table VII, and the strength of recommendations for the treatment of acne with hormonal agents is shown in Table III. World Health Organization (WHO) recommendations for COC usage eligibility are listed in Table VIII. Prescribing information for hormonal therapies is located in Supplementary Tables XXIII-XXVIII.

COCs have evolved since 1960. Ethinyl estradiol levels have gradually decreased from around 50 to 150 μg per pill to as low as 10 μg. A variety of different progestational moieties have been used, beginning with the first-generation progestins, the estranes (ie, norethindrone and ethynodiol diacetate). Second-generation progestins include levonorgestrel and norgestimate; these progestins are referred to as the gonanes. Third-generation progestins include less androgenic gonane progestins, such as desogestrel and gestodene. First-, second-, and third-generation progestins are derived from testosterone and alone have

androgenic potential. Fourth-generation progestins are not derived from testosterone and include the antiandrogenic progestin drospirenone. While progestins vary in their androgenic potential, evidence suggests that when combined with ethinyl estradiol, the net effect of all COCs is antiandrogenic.[219,220]

There are currently 4 COCs approved by the FDA for the treatment of acne. They are ethinyl estradiol/norgestimate, ethinyl estradiol/norethindrone acetate/ferrous fumarate, ethinyl estradiol/drospirenone, and ethinyl estradiol/drospirenone/levomefolate. The mechanism of action of COCs in the treatment of acne is based on their antiandrogenic properties. These pills 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-alfa-reductase activity and block the androgen receptor.[219,221-223]

Numerous randomized controlled clinical trials have assessed the efficacy of COCs in the management of acne.[98-101,221,224-226] It is evident from these trials that COCs reduce acne—both inflammatory and comedonal lesion counts. It is more difficult to determine which, if any, COC is consistently superior in the treatment of acne. A 2012 Cochrane metaanalysis assessed the effect of birth control pills on acne in women and included 31 trials with a total of 12,579 women. Nine trials compared a COC to placebo, and all of these COCs worked well to reduce acne. The progestins included in these 9 trials were levonorgestrel, norethindrone acetate, norgestimate, drospirenone, dienogest, and chlormadinone acetate. Seventeen trials compared 2 COCs, but no consistent differences in acne reduction were appreciated based on formulation or dosage of the COC. Only 1 small study compared a COC to an oral antibiotic; no significant difference in self-assessed acne improvement was identified.[221]

A recent publication evaluated the effectiveness of drospirenone 3 mg/ethinyl estradiol 20 μg in the treatment of moderate truncal AV. The COC showed significant reductions in inflammatory, noninflammatory, and total acne lesions compared to placebo.[227]

The risks of COCs must be weighed against the risks of the condition that they are treating or preventing. When COCs are used for contraception, their risks must be compared to the risks of pregnancy. 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.

COC use is associated with cardiovascular risks. Venous thromboembolic events (VTEs) have been the center of an ongoing debate regarding COCs. Traditionally, higher doses of ethinyl estradiol have been linked to increased risks of VTE. However, in recent years, some progestins have been implicated as risk factors for VTE. A recent Cochrane metaanalysis evaluated 25 publications reporting on 26 studies focused on oral contraceptives and venous thrombosis. The analysis concluded that all COC use increases the risk of VTE compared to nonusers. The relative risk of venous thrombosis for COCs with 30 to 35 μg of ethinyl estradiol and gestodene, desogestrel, cyproterone acetate, or drospirenone was similar and about 50% to 80% higher than for COCs with levonorgestrel.[228] To put this increased risk into perspective, it is important to note that the baseline risk of VTE in nonpregnant, nonusers of COCs is 1 to 5 per 10,000 woman-years. Users of COCs have a VTE risk of 3 to 9 per 10,000 woman-years. Users of drospirenone-containing COCs have a VTE risk of about 10 per 10,000 woman-years. Pregnant women have a VTE risk between 5 and 20 per 10,000 woman-years, and women within 12 weeks postpartum have a VTE risk of between 40 and 65 per 10,000 woman-years.[229,230]

Myocardial infarction (MI) risks are also increased in COC users. This risk is strongly associated with cigarette smoking and other risk factors, such as diabetes mellitus and hypertension. The WHO reports that COCs are not associated with an increased risk of MI in healthy, normotensive, nondiabetic, nonsmokers at any age.[231] There is also an increased risk of both ischemic and hemorrhagic stroke in COC users. Cigarette smoking and hypertension contribute to this increased risk, as do higher doses of ethinyl estradiol and age >35 years. While these are serious potential adverse events, these cardiovascular events are uncommon in women of reproductive age. An increased relative risk still translates to an overall low absolute risk.[219,222,232]

COC use may be associated with an increased risk of breast cancer in some women. A large metaanalysis including data from 53,297 women with breast cancer and 100,239 controls showed an increased risk of breast cancer in current users of COCs. The relative risk of breast cancer in current COC users was 1.24 (95% confidence interval [CI], 1.15-1.33). This increased risk disappeared 10 years after COC discontinuation. Age at first use of a COC was the only factor that was associated with an overall increased risk. Risk did not appear to

correlate with the duration of use of the COC or family history of breast cancer.[233] A more recent systematic review of cancer risks associated with oral contraceptive use also showed an increased relative risk (1.08; 95% CI, 1.00-1.17) of breast cancer in COC users, and higher risk was associated with more recent use of a COC.[234] Notably, this increased risk of breast cancer is greatest in women <34 years of age, when the overall incidence of breast cancer is at its lowest.[233]

The risk of cervical cancer may be increased in women who use COCs. An analysis of 24 observational studies found that the risk of cervical cancer increases with an increased duration of COC use. The risk declines after the COC is discontinued and the increase in risk disappears after 10 years of nonuse.[235] Another systematic review found no significant increase in the risk of cervical cancer among ever-users of COCs and never-users from 9 pooled studies. This study did show an increased risk of cervical cancer in women with >5 years of COC use compared with never-users, but the difference was not statistically significant.[234]

There is additional concern regarding COC use in younger adolescent populations given the adverse effects of low estrogen on bone mass. Peak bone mass development occurs during adolescence and young adulthood. The addition of low-dose estrogen COCs early in the teen years may undermine the accrual of bone mass.[236] Osteopenia or decreased bone mineral density with COC use has not been shown.[237,238] However, definitive conclusions are yet to be made. In general, the use of COC for acne should be avoided within 2 years of first starting menses or in patients who are <14 years of age unless it is clinically warranted. The FDA has approved COC use for females 14 years (eg, drospirenone and drosperinone/levomefolate) or 15 years (eg, norgestimate and norethindrone/ferrous fumarate) and older (and desiring use of a COC as mentioned above).

There are many noncontraceptive benefits of COCs in addition to the improvement of acne. These include regulation of the menstrual cycle, lessening of menorrhagia and associated anemia, and a reduction in the formation of benign ovarian tumors. Decreased risks of colorectal, ovarian, and endometrial cancers have been shown in COC users.[222,239]

Oral contraceptives may improve acne for many women. They may be used alone or in combination with other acne treatments. While some women present with signs or symptoms suggestive of a hormonally induced worsening of acne (ie, premenstrual flares or hirsutism), the use of COCs is not limited to these individuals. Any woman with signs or symptoms of hyperandrogenism should be evaluated appropriately for an underlying cause. However, COCs may be beneficial to women with clinical and laboratory findings of hyperandrogenism and in women without these findings.

COCs may be included as part of a comprehensive acne treatment regimen. Women who desire contraception or who suffer from menorrhagia may choose to begin a COC early in their acne treatment. In other women, COCs may be added to a treatment regimen when results with other agents have been limited. COCs may be used in combination with other oral acne medications, including the tetracycline class of antibiotics and spironolactone. There is much misunderstanding regarding the concomitant use of oral antibiotics and COCs and putative contraceptive failure. Rifampin and griseofulvin are the only antiinfectives that interact with COCs, lessening their effectiveness.[240] The tetracycline class of antibiotics has not been shown to reduce the effectiveness of COCs when taken concomitantly.[222,232,241,242]

Because the progestin drospirenone is an analog of spironolactone, there has been some concern that using a drospirenone-containing COC and spironolactone together might increase the risk of hyperkalemia. In 1 study, 27 women with acne were treated with a COC containing drospirenone 3 mg and ethinyl estradiol 30 μg and spironolactone 100 mg each day. There were no significant elevations of serum potassium and there were no additional side effects significant enough to discontinue treatment.[243]

Acne reduction with COC use takes time. Randomized controlled trials consistently show a statistically significant improvement in acne with COCs compared to placebo by the end of cycle 3.[98-101,224,225] Those treated with COCs for acne should be educated that acne reduction may not be appreciated for the first few months of treatment. Therefore, combining COCs with other acne medications early in treatment may be appropriate.

A Papanicolaou smear and a bimanual pelvic examination are no longer deemed mandatory before initiating the use of a COC. While these screening examinations may offer valuable information, they do not identify women who should not take a COC and should not be required before initiating treatment with a COC. Obtaining a thorough medical history and a blood pressure measurement are important before prescribing a COC.[244] Proper patient selection is imperative to minimize risks associated with COC use. The WHO

has published contraindications for the use of COCs.[245]

Spironolactone is an aldosterone receptor antagonist that exhibits potent antiandrogen activity by decreasing testosterone production and by competitively inhibiting binding of testosterone and dihydrotestosterone to androgen receptors in the skin.[246-249] It may also inhibit 5-alfa-reductase and increase steroid hormone–binding globulin.[250,251] Its use as an antiandrogen is not approved by the FDA for the treatment of acne. Two small, placebo-controlled prospective studies showed statistically significant improvement in acne severity and sebum production at doses ranging from 50 to 200 mg daily.[252,253] A retrospective chart review of 85 patients treated with spironolactone 50 to 100 mg daily, either as monotherapy or as adjunctive therapy, revealed that 66% of women were clear or markedly improved with favorable tolerability at these lower doses.[102] More recently, a Japanese study investigated the efficacy of spironolactone in Asian patients. One hundred thirty-nine Japanese patients (116 women and 23 men) were treated with spironolactone 200 mg daily for 8 weeks, followed by a taper of 50 mg every 4 weeks over a total of 20 weeks. All 64 women who completed the study had clinical improvement ranging from good to excellent. The study was discontinued prematurely in the male patients because of the development of gynecomastia.[103] Given the small number and size of available studies, a recent Cochrane database review concluded that there are insufficient data to support the efficacy of spironolactone in the treatment of acne.[254] Despite the lack of published data, relying on available evidence, experience, and expert opinion, the work group supports the use of spironolactone in the management of acne in select women.

Spironolactone is well tolerated overall, and its side effects are dose-related. Common side effects include diuresis (29%), menstrual irregularities (22%), breast tenderness (17%), breast enlargement, fatigue, headache, and dizziness.[255] Spironolactone is also pregnancy category C; animal studies have shown feminization of a male fetus early in gestation. Therefore, concomitant use of a COC is often recommended to both regulate menses and prevent pregnancy in many patients. Hyperkalemia is a potentially serious side effect that, fortunately, is rare in young healthy individuals with normal hepatic, adrenal, and renal function. Non–clinically relevant elevations may occur in about 13.7% of patients.[228] A recent retrospective database review identifying 967 women between 18 and 45 years of age taking spironolactone 50 to 200 mg daily for acne found that only 0.75% of the 1723 associated potassium measurements exceeded 5.0 mmol/L. Six of the 13 abnormal tests were normal upon repeat testing. Patients with renal or cardiovascular disease and those taking angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were excluded. Based on these findings, the authors concluded that testing for potassium in young healthy women taking spironolactone for acne is unnecessary.[256] Serum potassium testing is therefore not required, but should be considered in older patients and in patients who are also taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal antiinflammatory drugs, and digoxin. Measurements should be performed at baseline, during therapy, and after dose increases in these patients. Patients should also be educated about avoiding foods that are high in dietary potassium, such as low-sodium processed foods and coconut water.[257] Spironolactone may also be used safely with drospirenone-containing COCs. No elevations in serum potassium were identified in a series of 27 patients treated with spironolactone 100 mg daily in combination with ethinyl estradiol 30 μg/drospirenone 3 mg.[243]

Animal studies using up to 150 times human doses of spironolactone or its metabolite found the development of thyroid, hepatic, testicular, and breast adenomas, as well as thyroid carcinoma and myelocytic leukemia. These findings contributed to a black box warning stating that the off-label and unnecessary use of spironolactone should be avoided. To date, there has been only 1 human report suggesting carcinogenicity in which the authors identified 5 hospitalized patients with breast cancer who were taking spironolactone among other medications[258]; however, subsequent longitudinal and retrospective studies found no association.[255,259,260] In addition, a recent large retrospective matched cohort study of 1.29 million women >55 years of age found no association between spironolactone use and breast cancer with 8.4 million patient-years of use, further disproving any causal relationship.[261] These findings were supported by another large retrospective cohort study of 2.3 million women representing 28.8 million person-years that showed no association between spironolactone use and the development of breast, uterine, cervical, or ovarian cancers.[262]

Flutamide is a nonsteroidal selective androgen receptor blocker used in the treatment of prostate cancer. It is not approved by the FDA for use in acne. Doses ranging from 250 mg twice daily to as little as 62.5 mg daily have shown efficacy in the treatment of acne in small prospective trials.[104,263-267] Flutamide

Table IX. Recommendations for isotretinoin

Oral isotretinoin is recommended for the treatment of severe nodular acne
Oral isotretinoin is appropriate for the treatment of moderate acne that is treatment-resistant or for the management of acne that is producing physical scarring or psychosocial distress
Low-dose isotretinoin can be used to effectively treat acne and reduce the frequency and severity of medication-related side effects. Intermittent dosing of isotretinoin is not recommended
Routine monitoring of liver function tests, serum cholesterol, and triglycerides at baseline and again until response to treatment is established is recommended. Routine monitoring of complete blood count is not recommended
All patients treated with isotretinoin must adhere to the iPLEDGE risk management program
Females of child-bearing potential taking isotretinoin should be counseled regarding various contraceptive methods including user-independent forms
Prescribing physicians also should monitor their patients for any indication of inflammatory bowel disease and depressive symptoms and educate their patients about the potential risks with isotretinoin

250 mg twice daily combined with a triphasic COC reduced acne by 80% compared with spironolactone 50 mg twice daily/COC, which reduced acne by only 50% after 3 months of therapy.[245]

Common side effects associated with flutamide include gastrointestinal distress, breast tenderness, hot flashes, headache, xerosis, and decreased libido.[228,267] High rates of side effects among users may decrease compliance with use.[105] In 1 prospective randomized trial of 131 women, side effects at a dose of 125 mg daily were comparable to placebo.[267] Importantly, flutamide use has been associated with idiosyncratic fatal hepatotoxicity, which appears to be dose- and age-related.[268,269] Therefore, liver function tests need careful monitoring, and the risk of this serious adverse effect must be considered. Use of flutamide in the treatment of acne is discouraged except where benefit warrants the risk.

Low-dose prednisone in doses ranging from 5 to 15 mg daily, administered alone or with high-estrogen containing COCs, has shown efficacy in the treatment of acne and seborrhea.[106,270,271] However, long-term adverse effects of corticosteroids prohibit use as a primary therapy for acne. Prednisone in doses of 0.5 to 1 mg/kg/day is indicated for treatment of the systemic and cutaneous manifestations of acne fulminans and for treatment and prevention of isotretinoin-induced acne fulminans–like eruptions. A slow taper over several months is recommended while transitioning to isotretinoin or oral antibiotics in order to minimize relapses.[272,273]

Isotretinoin

Oral isotretinoin, an isomer of retinoic acid, has been used in the United States for the treatment of acne for >30 years and is approved by the FDA for the treatment of severe recalcitrant AV. Its use has proven successful for most patients with severe acne, resulting in decreased sebum production, acne lesions, and acne scarring, along with a decrease in symptoms of anxiety and depression.[107-117,274-277] It has also been effectively used in the treatment of moderate acne that is either treatment-resistant or that relapses quickly after the discontinuation of oral antibiotic therapy.[32,134-138] It is the consensus of the current working group that the presence of moderate acne that is either treatment-resistant, or that produces physical scarring or significant psychosocial distress, is an indication for treatment with oral isotretinoin. Recommendations for isotretinoin are shown in Table IX, and the strength of recommendations for treatment of acne with isotretinoin therapy is shown in Table III. Prescribing information for the treatment of acne with isotretinoin is listed in Supplementary Table XXIX.

When used for severe AV, isotretinoin is commonly initiated at a starting dose 0.5 mg/kg/day for the first month, then increased to 1.0 mg/kg/day thereafter as tolerated by the patient.[118] In extremely severe cases, even lower starting doses, with or without the concomitant use of oral steroids, may be needed. In earlier studies of optimal dosing of isotretinoin in patients with severe AV, doses ranging from 0.1 mg/kg/day to 1.0 mg/kg/day were most commonly used. Some efficacy was generally seen at all doses, along with a dose-dependent decrease in sebum production.[109] While there was not a significant difference in the improvement of acne by the end of the treatment course between doses of 0.5 and 1.0 mg/kg/day in most of the studies, there was a significant difference in relapse rates and the need for retreatment; patients treated with approximately 1.0 mg/kg/day had a significantly lower relapse rate and a lower rate of retreatment with isotretinoin than those treated with 0.5 mg/kg/day.[110,112,116] Similarly, a lower relapse rate was seen for those treated with a cumulative dose of >120 mg/kg compared to those treated with

<120 mg/kg.[110,119] It has been suggested that this dose-dependent therapeutic benefit plateaus beyond 150 mg/kg.[119] Therefore, in patients with severe AV, the work group supports 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.[278]

Isotretinoin treatment has been studied in patients with treatment-resistant or quick-relapsing, moderate AV. In this patient population, multiple studies have found that low-dose isotretinoin (0.25-0.4 mg/kg/day) is effective in the treatment of acne, and that this efficacy is comparable to the use of more conventional dosing.[32,107,134,135,279] This may also be true for a low cumulative dose regimen.[136] In addition, low-dose regimens are associated with a decreased rate of medication-related adverse effects, thereby leading to improved tolerability and increased patient satisfaction.[107,134,135,279,280] Unlike in patients with severe acne, relapse rates in patients with moderate acne treated with low-dose isotretinoin are equal to relapse rates in those treated with conventional dosing.[32,279] Intermittent dosing, however, is not as effective and is associated with higher relapse rates; therefore, it is not recommended.[32,134,135,276]

Isotretinoin is highly lipophilic and is best absorbed when taken with food.[115,120,121] Patients should be instructed to take isotretinoin with meals. One formulation, isotretinoin with lidose, uses lipid agents to encase the medication, bypassing the need for food, and can be taken on an empty stomach.[121]

Common adverse effects associated with the intake of isotretinoin have been well documented and reviewed in previous guidelines.[1] The most prevalent side effects involve the mucocutaneous, musculoskeletal, and ophthalmic systems, generally mimicking symptoms of hypervitaminosis A. With standard courses, these side effects are temporary and resolve without sequelae after discontinuation of the drug. Other real and speculative adverse effects of interest include inflammatory bowel disease, depression/anxiety/mood changes, cardiovascular risk factors, bone mineralization, concerns regarding scarring, and *S aureus* colonization.

Inflammatory bowel disease (IBD) consists of ulcerative colitis (UC) and Crohn disease (CD). Several retrospective analyses have been performed to determine whether there is an association between isotretinoin intake and IBD.[122-126,281,282] While 2 studies[123,282] have shown a potential relationship, more recent analyses[122,125,283] suggest no association between IBD and isotretinoin ingestion. The most convincing article suggesting an association between isotretinoin and UC[124] was directly refuted by a later analysis of the same database.[125] Therefore, the work group agrees with the position statement of the American Academy of Dermatology that the "current evidence is insufficient to prove either an association or causal relationship between isotretinoin use and IBD."[284]

Changes in mood, including depression, suicidal ideation, and suicide have been reported sporadically in patients who are taking isotretinoin.[127,285] To date, no studies to suggest an evidence-based link between isotretinoin and depression, anxiety, mood changes, or suicidal ideation/suicide exist. Multiple studies have shown no evidence of depression from isotretinoin on a population basis.[128-133,137,285] On the contrary, most studies have shown isotretinoin to improve or have no negative effects on mood, memory, attention, or executive functions.[113,128-133,137,285-288] However, 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 and make therapeutic decisions within the context of each individual patient.

Physicians prescribing isotretinoin need to be aware of guidelines for evidence-based monitoring of side effects. Interest in bone demineralization and premature epiphyseal closure observed with long-term oral retinoid intake led to early concerns about these issues for patients taking isotretinoin for acne. While premature epiphyseal closure has been reported in 2 isolated patients who were taking short-term isotretinoin for acne,[289,290] these effects have not been reported in any other studies of patients taking short-term isotretinoin therapy for AV.[119,139] It remains the opinion of this work group that routine screening for these issues is not required in patients who are taking short-term isotretinoin therapy. Serum cholesterol and triglycerides, as well as transaminases, have been known to rise in some patients taking oral isotretinoin.[140-142] While there is no proof of long-term cardiovascular risk from short-term elevation of triglycerides and cholesterol during short-term isotretinoin therapy,[140] the routine monitoring of serum lipid profiles and liver function studies should continue.[139,142,291,292] This work group could find no evidence-based reason that routine monitoring of complete blood cell counts is warranted.

Table X. Recommendations for miscellaneous therapies and physical modalities

There is limited evidence to recommend the use and benefit of physical modalities for the routine treatment of acne, including pulsed dye laser, glycolic acid peels, and salicylic acid peels
Intralesional corticosteroid injections are effective in the treatment of individual acne nodules

Several early case series described delayed wound healing or keloid formation in patients who were taking or had recently taken isotretinoin, leading to the current recommendation to delay procedures such as dermabrasion or laser resurfacing until 6 to 12 months after discontinuing isotretinoin.[293,294] Recent prospective small interventional studies did not find atypical scarring with chemical peels or manual dermabrasion in any patient currently or recently on isotretinoin.[291,294] There are also retrospective studies and case reports demonstrating safety with laser hair removal, pulsed dye laser, and CO_2 laser.[295-299] While elective procedures should be delayed for 6 to 12 months when possible, careful consideration may be given on a case by case basis.

Higher rates of colonization with *S aureus* have been seen in patients taking systemic isotretinoin, leading to increased rates of minor skin infections, such as folliculitis and furunculosis.[300,301] On rare occasions, the combination of cheilitis and *S aureus* colonization can cause lip or perioral abscesses, a serious complication requiring prompt attention.[300]

The teratogenic effects of isotretinoin and the risk for retinoic acid embryopathy are well known. After introduction of isotretinoin in the United States in 1982, there were hundreds of reports of isotretinoin-exposed pregnancies within just several years, resulting in a high rate of congenital malformations.[302] Because of this, the first risk management program was implemented. iPLEDGE is now the third risk management program that has been put in place in an effort to prevent isotretinoin exposure during pregnancy. As mandated by the FDA, all patients receiving isotretinoin—both men and women—are required to enroll in and adhere to the iPLEDGE risk management program. Despite this, fetal exposure has not significantly decreased since the implementation of iPLEDGE, and approximately 150 isotretinoin-exposed pregnancies still occur in the United States each year[143,144] because of noncompliance with the iPLEDGE contraceptive requirements to abstain from sex or to use 2 contraceptive methods. Nearly one-third of all women of childbearing potential in a recent US study admitted noncompliance with iPLEDGE pregnancy prevention requirements; of those that were sexually active, 29% did not comply with the use of condoms that they had agreed to use as 1 of their methods, and 39% missed ≥1 contraceptive pills in the previous month.[144] Therefore, every woman of child-bearing potential taking isotretinoin should be carefully counseled regarding various contraceptive methods that are available and the specific requirements of the iPLEDGE system at each clinic visit. Patient-independent forms of birth control, including long-acting reversible contraceptives, should be considered whenever appropriate.

MISCELLANEOUS THERAPIES/PHYSICAL MODALITIES

There is limited evidence published in the peer-reviewed medical literature that addresses the efficacy of comedo removal for the treatment of acne despite its long-standing clinical use. It is, however, the opinion of the work group that comedo removal is often helpful in the management of comedones that are resistant to other therapies. Recommendations for miscellaneous therapies and physical modalities are listed in Table X, and the strength of recommendations for treatment of acne using miscellaneous therapies and physical modalities is shown in Table III. Prescribing information for miscellaneous therapies and physical modalities is located in Supplementary Tables XXX-XXXIII.

Studies exist suggesting that chemical peels may improve acne. However, large, multicenter, double-blinded control trials comparing peels to placebo and comparing different peels are lacking. Glycolic acid and salicylic acid chemical peels may be helpful for noninflammatory (comedonal) lesions.[145-147,303,304] However, multiple treatments are needed and the results are not long-lasting. In the opinion of the work group, chemical peels may result in mild improvement in comedonal acne.

Some laser and light devices may be beneficial for acne, but additional studies are needed. Studies exist evaluating the use of many lasers, including pulsed dye laser, potassium titanyl phosphate (KTP) laser, fractionated and nonfractionated infrared lasers, and the fractionated CO_2 laser. Light devices aside from lasers have also been investigated, including radiofrequency, intense pulsed light, photopneumatic therapy, and photodynamic therapy (PDT).

Table XI. Recommendation for complementary/alternative therapies

Herbal and alternative therapies have been used to treat acne. Although most of these products appear to be well tolerated, limited data exist regarding the safety and efficacy of these agents to recommend their use in acne

Of all laser and light devices, the most evidence exists for PDT in treating acne.[305-308] With PDT, a photosensitizer, such as aminolevulinic acid, is first applied to the affected skin for a period of time (varying from 15 minutes to 3 hours). The photosensitizer is then absorbed into the pilosebaceous units and is preferentially taken up by sebocytes. A laser or light device is then used to activate the photosensitizer, generating singlet oxygen species, and thereby damaging the sebaceous glands and reducing *P acnes*. This treatment shows great promise, but additional studies are needed to determine the optimal photosensitizer, incubation time, and light source.

Intralesional injection of triamcinolone acetonide is a commonly used technique for the management of larger, nodular lesions in patients with acne.[148,149] Rapid improvement and decreased pain are noted. Local atrophy, systemic absorption of steroids, and possible adrenal suppression may occur.[309] Decreasing the concentration and the volume of steroid used will minimize these complications.

COMPLEMENTARY/ALTERNATIVE THERAPIES

Two clinical trials have shown that topical tea tree oil is effective for the treatment of acne.[150,151] In 1 study, it was comparable to BP but better tolerated. Other herbal agents, such as topical and oral ayurvedic compounds, oral barberry extract, and gluconolactone solution have been reported to have value in the treatment of acne.[152-155]

The psychological effects of acne may be profound, and it is the opinion of the expert work group that effective acne treatment can improve the emotional outlook of patients. There is weak evidence of the possible benefit of biofeedback-assisted relaxation and cognitive imagery.[156,310]

The recommendation for using complementary and alternative therapies is listed in Table XI, and the strength of recommendation for treatment of acne using complementary and alternative therapies is shown in Table III.

ROLE OF DIET IN ACNE

Emerging evidence suggests that high glycemic index diets may be associated with acne. In 2007, a randomized controlled trial with 23 Australian males 15 to 25 years of age examined the impact of a low glycemic diet on acne. Those randomized to follow the low glycemic load (LGL) diet had significant improvement in acne severity, a significant reduction in weight and body mass index (BMI), a significant decrease in free androgen index, and improved insulin sensitivity at the end of 12 weeks.[157] The study was limited by its small sample size and the fact that both groups lost weight. In 2012, a 10-week randomized controlled trial was conducted in 32 Korean subjects (24 men and 8 women) 20 to 27 years of age. Those randomized to the LGL diet had a statistically significant improvement in acne severity and no change in weight and BMI. Histologic analyses were conducted, and the authors found that the size of the sebaceous glands were significantly reduced in the LGL group, whereas hematoxylin–eosin stains revealed a decrease in inflammatory cells and additional stains showed a decrease in inflammatory cytokines.[158] Although these 2 studies are the most rigorous to date analyzing the effect of glycemic index diets on acne, a small number of studies further support this association.[159-161,311]

Table XII. Recommendations for the role of diet in acne

Given the current data, no specific dietary changes are recommended in the management of acne
Emerging data suggest that high glycemic index diets may be associated with acne
Limited evidence suggests that some dairy, particularly skim milk, may influence acne

While no randomized controlled trials have been conducted to examine the role of dairy consumption and acne, several observational studies suggest that certain dairy products, especially skim milk, may aggravate acne. In 2005, a retrospective study analyzed data from 47,355 adult women who were asked to recall their high school diet. They were also asked to recall if they had "physician-diagnosed acne." In this study, acne was positively associated with the reported quantity of milk ingestion. The strongest association was noted with skim milk. Specifically, women who consumed ≥2 glasses of skim milk a day had a 44% increased risk of reporting acne.[312] This study was heavily criticized for its retrospective design, so the same research group conducted 2 follow-up, prospective studies. The first

Table XIII. Research and knowledge gaps in acne

Topics	Identified research gaps
General	Treatment of acne in persons of color
	Treatment of acne in pregnant women
Pathogenesis	Molecular and cellular mechanisms underlying acne
	Molecular description of postinflammatory hyperpigmentation
	Pathophysiology of acne scar, both atrophic and hypertrophic types
	Immunopathogenesis of acne
Grading and classification	Develop assessment tools that better help characterize acne in the office
	Develop and validate patient-reported outcome measures for assessing acne treatment in office/clinic
Topical therapies	Efficacy, safety, and side effect profile of topical therapies in children 8-12 years of age
	Data on aspects of care that promote compliance in selected populations using topical therapy
	The incidence of cutaneous and systemic allergic response to topical therapies remains to be better quantified in the population
Systemic antibiotics	Comparative studies on duration of oral antibiotics with and without topical treatment
Hormonal agents	Comparative studies on the duration of hormonal therapies with and without topical treatment
	Large, prospective studies to confirm the efficacy of spironolactone for the treatment of postadolescent acne in women
	Comparative effectiveness clinical trials of COCs in the treatment of acne
	Standardization of workup for patients with hormonal acne in whom PCOS is suspected
Isotretinoin	Long-term prospective studies to determine if there is a causal link between isotretinoin and depression
	Long-term prospective studies to determine if there is a causal link between isotretinoin and inflammatory bowel disease
	Studies of best methods for preventing isotretinoin-exposed pregnancies
	Prospective studies examining optimal total cumulative dosing based on type and severity of acne
Physical modalities	Large, prospective, multicenter, randomized, double-blinded controlled trials comparing acne chemical peels to placebo
	Comparative effectiveness clinical trials for safety and efficacy of different peels
	Large, prospective, multicenter, randomized, double-blinded controlled trials comparing light and laser devices to placebo
	Comparative effectiveness clinical trials for safety and efficacy of different light and laser sources/wavelengths and which types of lesions they improve
Role of diet in acne	Long-term, prospective, double-blind trials looking at the effect of low-glycemic index diet and milk (skim vs. whole) on acne
	Prospective studies of fish oil, probiotics, oral zinc, and topical tea tree oil

COC, Combined oral contraceptive; *PCOS*, polycystic ovarian syndrome.

was conducted on a cohort of girls, and found that acne was associated with total milk intake, whole milk, low-fat milk, and skim milk.[162] The second study focused on boys only, and found that acne was associated with the intake of skim milk only.[163] More recently, a case control study involving 88 Malaysian subjects 18 to 30 years of age found that the frequency of milk and ice cream consumption was significantly higher in patients with acne compared to controls.[161] Dermatologist-assessed subjects who consumed milk or ice cream ≥1 time per week had a 4-fold increased risk of having acne. No association was found with cheese or yogurt. Also in 2012, another case control study involving 563 Italian subjects 10 to 24 years of age found that the risk of acne was also increased with milk consumption.[164] The association was more marked with skim milk, and again no association was seen with cheese or yogurt.

Although some small preliminary studies have examined the role of antioxidants (including oral zinc[313]), probiotics,[314] and fish oil[315] on acne, the existing evidence is not strong enough to support any recommendations regarding these dietary factors at this time. Recommendations for the role of diet in acne are listed in Table XII, and the strength of recommendations for the role of diet in acne is shown in Table III.

GAPS IN RESEARCH/KNOWLEDGE

We have described above the significant progress that has been made in understanding the pathogenesis and treatment of acne, but there are still large gaps in our knowledge base. In Table XIII, we address some of the most important current gaps in research.

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Hilary E. Baldwin, MD, served on the Advisory Board of Allergan Inc, receiving honoraria. Dr Baldwin also served as a speaker for Galderma Laboratories, GlaxoSmithKline, Ranbaxy Laboratories Ltd, and Valeant Pharmaceutical International, receiving honoraria. Diane S. Berson, MD, served on the Advisory Board of Galderma Laboratories, La-Roche-Posay Laboratoire Pharmaceutique, and Medicis Pharmaceutical Corporation, receiving honoraria. Dr Berson also served as a consultant for Procter & Gamble, receiving honoraria. Whitney Bowe, MD, served on the Advisory Board of Allergan, Inc, Galderma Laboratories, and Johnson & Johnson Consumer Products Company, receiving honoraria. Dr Bowe also served as a speaker for Bayer and consultant for Galderma Laboratories, Johnson & Johnson Consumer Products Company, L'Oréal USA Inc, Onset Therapeutics, and Procter & Gamble, receiving honoraria. Dr Bowe also received honoraria from Energizer Holdings, Inc. Julie C. Harper, MD, served as speaker for Allergan, Inc, Coria Laboratories, Galderma USA, La-Roche-Posay Laboratoire Pharmaceutique, Promius Pharma, LLC, and Valeant Pharmaceutical North America, receiving honoraria. Dr Harper served on the Advisory Board for Stiefel, receiving honoraria. Dr Harper served as consultant to Galderma Laboratories and Stiefel, receiving honoraria. Dr Harper also received other honoraria from Bayer Pharmaceuticals. Sewon Kang, MD, served on the Advisory Board for Dermira, receiving stock options, and the Advisory Board for Galderma Laboratories, Pfizer, Inc, and Unilever Home & Personal Care USA, receiving honoraria. Jonette E. Keri, MD, PhD, served on the Advisory Board for Suneva Medical, Inc, receiving honoraria. Dr Keri also served as consultant for F. Hoffmann-La Roche AG, receiving honoraria. James J. Leyden, MD, served as consultant for Allergan, Inc, Anacor Pharmaceuticals Inc, Cipher Pharmaceuticals, Combe Inc, Galderma Laboratories, Medicis Pharmaceutical Corporation, Obagi Medical Products, and Unilever Home & Personal Care USA, receiving honoraria. Rachel V. Reynolds, MD, served as consultant for Biosense Webster and Medtronics. Nanette Silverberg, MD, served on the Advisory Board for Leo Pharma, Inc, receiving honoraria. Dr Silverberg also served as consultant for Johnson & Johnson Consumer Products Company, receiving honoraria. Linda F. Stein Gold, MD, served on the Advisory Board for AbbVie, Galderma Laboratories, LEO Pharma, US, Lilly ICOS LLC, Medicis Pharmaceutical Corporation, Pfizer Inc, Stiefel, Taro Pharm, Valeant Pharmaceuticals International, and Warner Chilcott, receiving honoraria. Dr Stein Gold also served as speaker for Actavis and Warner Chilcott and consultant for Ferndale Laboratories, receiving honoraria. Dr Stein Gold also received other honoraria from Roche Laboratories. Jonathan S. Weiss, MD, served on the Advisory Board for Galderma Laboratories and Valeant Pharmaceuticals International, receiving honoraria. Dr Weiss also served as consultant for Abbott Laboratories, Celgene Corporation, LEO Pharma, and Sebcaia, Inc, receiving honoraria. Andrea L. Zaenglein, MD, served on the Advisory Board for Anacor Pharmaceuticals, Galderma Laboratories, Promius Pharmaceuticals, and Valeant Pharmaceuticals International, receiving honoraria. Dr Zaenglein also served as consultant for Ranbaxy Laboratories Limited, receiving honoraria. Arun L. Pathy, MD, Ali Alikhan, MD, Emmy M. Graber, MD, Bethanee J. Schlosser, MD, PhD, Megha M. Tollefson, MD, Nancy Dolan, MD, Andy Sagan, MD, Mackenzie Stern, Kevin M. Boyer, MPH, and Reva Bhushan, MA, PhD, have no relevant relationships to disclose.

REFERENCES

1. Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. *J Am Acad Dermatol*. 2007;56:651-663.
2. Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics*. 2013;131(suppl 3):S163-S186.
3. Ebell MH, Siwek J, Weiss BD, et al. Simplifying the language of evidence to improve patient care: Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in medical literature. *J Fam Pract*. 2004;53:111-120.
4. American Academy of Dermatology website. Guideline development process. Available at: https://www.aad.org/practice-tools/quality-care/clinical-guidelines/guideline-development-process. Accessed January 4, 2016.

5. White GM. Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. *J Am Acad Dermatol*. 1998;39:S34-S37.
6. Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol*. 2013;168:474-485.
7. Goulden V, Stables GI, Cunliffe WJ. Prevalence of facial acne in adults. *J Am Acad Dermatol*. 1999;41:577-580.
8. Tan JK, Tang J, Fung K, et al. Development and validation of a comprehensive acne severity scale. *J Cutan Med Surg*. 2007; 11:211-216.
9. Mallon E, Newton JN, Klassen A, et al. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. *Br J Dermatol*. 1999;140:672-676.
10. Gupta MA, Johnson AM, Gupta AK. The development of an Acne Quality of Life scale: reliability, validity, and relation to subjective acne severity in mild to moderate acne vulgaris. *Acta Derm Venereol*. 1998;78:451-456.
11. Lasek RJ, Chren MM. Acne vulgaris and the quality of life of adult dermatology patients. *Arch Dermatol*. 1998;134:454-458.
12. Martin AR, Lookingbill DP, Botek A, et al. Health-related quality of life among patients with facial acne—assessment of a new acne-specific questionnaire. *Clin Exp Dermatol*. 2001; 26:380-385.
13. Rapp SR, Feldman SR, Graham G, et al. The Acne Quality of Life Index (Acne-QOLI): development and validation of a brief instrument. *Am J Clin Dermatol*. 2006;7:185-192.
14. Dreno B, Khammari A, Orain N, et al. ECCA grading scale: an original validated acne scar grading scale for clinical practice in dermatology. *Dermatology*. 2007;214:46-51.
15. Pochi PE, Shalita AR, Strauss JS, et al. Report of the Consensus Conference on Acne Classification. Washington, D.C., March 24 and 25, 1990. *J Am Acad Dermatol*. 1991;24:495-500.
16. Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. *Int J Dermatol*. 1997;36:416-418.
17. Lucky AW, Barber BL, Girman CJ, et al. A multirater validation study to assess the reliability of acne lesion counting. *J Am Acad Dermatol*. 1996;35:559-565.
18. Cook CH, Centner RL, Michaels SE. An acne grading method using photographic standards. *Arch Dermatol*. 1979;115: 571-575.
19. Burke BM, Cunliffe WJ. The assessment of acne vulgaris—the Leeds technique. *Br J Dermatol*. 1984;111:83-92.
20. Allen BS, Smith JG Jr. Various parameters for grading acne vulgaris. *Arch Dermatol*. 1982;118:23-25.
21. Dreno B, Poli F, Pawin H, et al. Development and evaluation of a Global Acne Severity Scale (GEA Scale) suitable for France and Europe. *J Eur Acad Dermatol Venereol*. 2011;25:43-48.
22. Hayashi N, Akamatsu H, Kawashima M. Acne Study Group. Establishment of grading criteria for acne severity. *J Dermatol*. 2008;35:255-260.
23. Hayashi N, Suh DH, Akamatsu H, Kawashima M, Acne Study Group. Evaluation of the newly established acne severity classification among Japanese and Korean dermatologists. *J Dermatol*. 2008;35:261-263.
24. Tan J, Wolfe B, Weiss J, et al. Acne severity grading: determining essential clinical components and features using a Delphi consensus. *J Am Acad Dermatol*. 2012;67:187-193.
25. Tan JK, Jones E, Allen E, et al. Evaluation of essential clinical components and features of current acne global grading scales. *J Am Acad Dermatol*. 2013;69:754-761.
26. Beylot C, Chivot M, Faure M, et al. Inter-observer agreement on acne severity based on facial photographs. *J Eur Acad Dermatol Venereol*. 2010;24:196-198.
27. Tan JK, Fung K, Bulger L. Reliability of dermatologists in acne lesion counts and global assessments. *J Cutan Med Surg*. 2006;10:160-165.
28. Bergman H, Tsai KY, Seo SJ, Kvedar JC, Watson AJ. Remote assessment of acne: the use of acne grading tools to evaluate digital skin images. *Telemed J E Health*. 2009;15:426-430.
29. Min S, Kong HJ, Yoon C, Kim HC, Suh DH. Development and evaluation of an automatic acne lesion detection program using digital image processing. *Skin Res Technol*. 2013;19: e423-e432.
30. Qureshi AA, Brandling-Bennett HA, Giberti S, et al. Evaluation of digital skin images submitted by patients who received practical training or an online tutorial. *J Telemed Telecare*. 2006;12:79-82.
31. Choi CW, Choi JW, Park KC, Youn SW. Ultraviolet-induced red fluorescence of patients with acne reflects regional casual sebum level and acne lesion distribution: qualitative and quantitative analyses of facial fluorescence. *Br J Dermatol*. 2012;166:59-66.
32. Choi CW, Lee DH, Kim HS, et al. The clinical features of late onset acne compared with early onset acne in women. *J Eur Acad Dermatol Venereol*. 2011;25:454-461.
33. Dobrev H. Fluorescence diagnostic imaging in patients with acne. *Photodermatol Photoimmunol Photomed*. 2010;26: 285-289.
34. Choi CW, Choi JW, Youn SW. Subjective facial skin type, based on the sebum related symptoms, can reflect the objective casual sebum level in acne patients. *Skin Res Technol*. 2013;19:176-182.
35. Kim MK, Choi SY, Byun HJ, et al. Comparison of sebum secretion, skin type, pH in humans with and without acne. *Arch Dermatol Res*. 2006;298:113-119.
36. Xhauflaire-Uhoda E, Pierard GE. Skin capacitance imaging of acne lesions. *Skin Res Technol*. 2007;13:9-12.
37. Youn SH, Choi CW, Choi JW, Youn SW. The skin surface pH and its different influence on the development of acne lesion according to gender and age. *Skin Res Technol*. 2013;19: 131-136.
38. Youn SW, Kim JH, Lee JE, Kim SO, Park KC. The facial red fluorescence of ultraviolet photography: is this color due to Propionibacterium acnes or the unknown content of secreted sebum? *Skin Res Technol*. 2009;15:230-236.
39. Zane C, Capezzera R, Pedretti A, Facchinetti E, Calzavara-Pinton P. Non-invasive diagnostic evaluation of phototherapeutic effects of red light phototherapy of acne vulgaris. *Photodermatol Photoimmunol Photomed*. 2008;24: 244-248.
40. Cove JH, Cunliffe WJ, Holland KT. Acne vulgaris: is the bacterial population size significant? *Br J Dermatol*. 1980; 102:277-280.
41. Mourelatos K, Eady EA, Cunliffe WJ, Clark SM, Cove JH. Temporal changes in sebum excretion and propionibacterial colonization in preadolescent children with and without acne. *Br J Dermatol*. 2007;156:22-31.
42. Shaheen B, Gonzalez M. A microbial aetiology of acne: what is the evidence? *Br J Dermatol*. 2011;165:474-485.
43. Fitz-Gibbon S, Tomida S, Chiu BH, et al. Propionibacterium acnes strain populations in the human skin microbiome associated with acne. *J Invest Dermatol*. 2013;133:2152-2160.
44. Holland C, Mak TN, Zimny-Arndt U, et al. Proteomic identification of secreted proteins of Propionibacterium acnes. *BMC Microbiol*. 2010;10:230.
45. Lomholt HB, Kilian M. Population genetic analysis of *Propionibacterium acnes* identifies a subpopulation and

epidemic clones associated with acne. *PLoS One*. 2010;5:e12277.
46. Miura Y, Ishige I, Soejima N, et al. Quantitative PCR of Propionibacterium acnes DNA in samples aspirated from sebaceous follicles on the normal skin of subjects with or without acne. *J Med Dent Sci*. 2010;57:65-74.
47. Tochio T, Tanaka H, Nakata S, Ikeno H. Accumulation of lipid peroxide in the content of comedones may be involved in the progression of comedogenesis and inflammatory changes in comedones. *J Cosmet Dermatol*. 2009;8:152-158.
48. Tomida S, Nguyen L, Chiu BH, et al. Pan-genome and comparative genome analyses of propionibacterium acnes reveal its genomic diversity in the healthy and diseased human skin microbiome. *MBio*. 2013;4:e00003-e00013.
49. Lucky AW, Biro FM, Simbartl LA, Morrison JA, Sorg NW. Predictors of severity of acne vulgaris in young adolescent girls: results of a five-year longitudinal study. *J Pediatr*. 1997;130:30-39.
50. Bunker CB, Newton JA, Kilborn J, et al. Most women with acne have polycystic ovaries. *Br J Dermatol*. 1989;121:675-680.
51. Lawrence DM, Katz M, Robinson TW, et al. Reduced sex hormone binding globulin and derived free testosterone levels in women with severe acne. *Clin Endocrinol*. 1981;15:87-91.
52. Timpatanapong P, Rojanasakul A. Hormonal profiles and prevalence of polycystic ovary syndrome in women with acne. *J Dermatol*. 1997;24:223-229.
53. Lucky AW. Endocrine aspects of acne. *Pediatr Clin North Am*. 1983;30:495-499.
54. Lucky AW, McGuire J, Rosenfield RL, Lucky PA, Rich BH. Plasma androgens in women with acne vulgaris. *J Invest Dermatol*. 1983;81:70-74.
55. Abulnaja KO. Changes in the hormone and lipid profile of obese adolescent Saudi females with acne vulgaris. *Braz J Med Biol Res*. 2009;42:501-505.
56. Arora MK, Seth S, Dayal S. The relationship of lipid profile and menstrual cycle with acne vulgaris. *Clin Biochem*. 2010;43:1415-1420.
57. Fyrand O, Jakobsen HB. Water-based versus alcohol-based benzoyl peroxide preparations in the treatment of acne vulgaris. *Dermatologica*. 1986;172:263-267.
58. Mills OH Jr, Kligman AM, Pochi P, Comite H. Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. *Int J Dermatol*. 1986;25:664-667.
59. Schutte H, Cunliffe WJ, Forster RA. The short-term effects of benzoyl peroxide lotion on the resolution of inflamed acne lesions. *Br J Dermatol*. 1982;106:91-94.
60. Mills O Jr, Thornsberry C, Cardin CW, Smiles KA, Leyden JJ. Bacterial resistance and therapeutic outcome following three months of topical acne therapy with 2% erythromycin gel versus its vehicle. *Acta Derm Venereol*. 2002;82:260-265.
61. Bernstein JE, Shalita AR. Topically applied erythromycin in inflammatory acne vulgaris. *J Am Acad Dermatol*. 1980;2:318-321.
62. Jones EL, Crumley AF. Topical erythromycin vs blank vehicle in a multiclinic acne study. *Arch Dermatol*. 1981;117:551-553.
63. Shalita AR, Smith EB, Bauer E. Topical erythromycin v clindamycin therapy for acne. A multicenter, double-blind comparison. *Arch Dermatol*. 1984;120:351-355.
64. Leyden JJ, Shalita AR, Saatjian GD, Sefton J. Erythromycin 2% gel in comparison with clindamycin phosphate 1% solution in acne vulgaris. *J Am Acad Dermatol*. 1987;16:822-827.
65. Kuhlman DS, Callen JP. A comparison of clindamycin phosphate 1 percent topical lotion and placebo in the treatment of acne vulgaris. *Cutis*. 1986;38:203-206.
66. Becker LE, Bergstresser PR, Whiting DA, et al. Topical clindamycin therapy for acne vulgaris. A cooperative clinical study. *Arch Dermatol*. 1981;117:482-485.
67. Leyden JJ, Hickman JG, Jarratt MT, Stewart DM, Levy SF. The efficacy and safety of a combination benzoyl peroxide/clindamycin topical gel compared with benzoyl peroxide alone and a benzoyl peroxide/erythromycin combination product. *J Cutan Med Surg*. 2001;5:37-42.
68. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. *J Am Acad Dermatol*. 1997;37:590-595.
69. Tschen EH, Katz HI, Jones TM, et al. A combination benzoyl peroxide and clindamycin topical gel compared with benzoyl peroxide, clindamycin phosphate, and vehicle in the treatment of acne vulgaris. *Cutis*. 2001;67:165-169.
70. Krishnan G. Comparison of two concentrations of tretinoin solution in the topical treatment of acne vulgaris. *Practitioner*. 1976;216:106-109.
71. Bradford LG, Montes LF. Topical application of vitamin A acid in acne vulgaris. *South Med J*. 1974;67:683-687.
72. Shalita AR, Chalker DK, Griffith RF, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. *Cutis*. 1999;63:349-354.
73. Shalita A, Weiss JS, Chalker DK, et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. *J Am Acad Dermatol*. 1996;34:482-485.
74. Cunliffe WJ, Caputo R, Dreno B, et al. Clinical efficacy and safety comparison of adapalene gel and tretinoin gel in the treatment of acne vulgaris: Europe and U.S. multicenter trials. *J Am Acad Dermatol*. 1997;36(6 pt 2):S126-S134.
75. Richter JR, Bousema MT, De Boulle KLV, Degreef HJ, Poli F. Efficacy of a fixed clindamycin phosphate 1.2%, tretinoin 0.025% gel formulation (Velac) in the topical control of facial acne lesions. *J Dermatolog Treat*. 1998;9:81-90.
76. Zouboulis CC, Derumeaux L, Decroix J, Maciejewska-Udziela B, Cambazard F, Stuhlert A. A multicentre, single-blind, randomized comparison of a fixed clindamycin phosphate/tretinoin gel formulation (Velac) applied once daily and a clindamycin lotion formulation (Dalacin T) applied twice daily in the topical treatment of acne vulgaris. *Br J Dermatol*. 2000;143:498-505.
77. Christiansen JV, Gadborg E, Ludvigsen K, et al. Topical tretinoin, vitamin A acid (Airol) in acne vulgaris. A controlled clinical trial. *Dermatologica*. 1974;148:82-89.
78. Dunlap FE, Mills OH, Tuley MR, Baker MD, Plott RT. Adapalene 0.1% gel for the treatment of acne vulgaris: its superiority compared to tretinoin 0.025% cream in skin tolerance and patient preference. *Br J Dermatol*. 1998;139(suppl 52):17-22.
79. Kakita L. Tazarotene versus tretinoin or adapalene in the treatment of acne vulgaris. *J Am Acad Dermatol*. 2000;43:S51-S54.
80. Webster GF, Berson D, Stein LF, Fivenson DP, Tanghetti EA, Ling M. Efficacy and tolerability of once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.025% gel in the treatment of facial acne vulgaris: a randomized trial. *Cutis*. 2001;67:4-9.
81. Galvin SA, Gilbert R, Baker M, Guibal F, Tuley MR. Comparative tolerance of adapalene 0.1% gel and six

different tretinoin formulations. *Br J Dermatol*. 1998; 139(suppl 52):34-40.
82. Cunliffe WJ, Holland KT. Clinical and laboratory studies on treatment with 20% azelaic acid cream for acne. *Acta Derm Venereol Suppl (Stockh)*. 1989;143:31-34.
83. Katsambas A, Graupe K, Stratigos J. Clinical studies of 20% azelaic acid cream in the treatment of acne vulgaris. Comparison with vehicle and topical tretinoin. *Acta Derm Venereol Suppl (Stockh)*. 1989;143:35-39.
84. Draelos ZD, Carter E, Maloney JM, et al. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. *J Am Acad Dermatol*. 2007;56:439.e1-439.e10.
85. Lucky AW, Maloney JM, Roberts J, et al. Dapsone gel 5% for the treatment of acne vulgaris: safety and efficacy of long-term (1 year) treatment. *J Drugs Dermatol*. 2007;6: 981-987.
86. Tanghetti E, Harper JC, Oefelein MG. The efficacy and tolerability of dapsone 5% gel in female vs male patients with facial acne vulgaris: gender as a clinically relevant outcome variable. *J Drugs Dermatol*. 2012;11:1417-1421.
87. Shalita AR. Treatment of mild and moderate acne vulgaris with salicylic acid in an alcohol-detergent vehicle. *Cutis*. 1981; 28:556-558, 561.
88. Garner SE, Eady A, Bennett C, Newton JN, Thomas K, Popescu CM. Minocycline for acne vulgaris: efficacy and safety. *Cochrane Database Syst Rev*. 2012;(8):CD002086.
89. Leyden JJ, Bruce S, Lee CS, et al. A randomized, phase 2, dose-ranging study in the treatment of moderate to severe inflammatory facial acne vulgaris with doxycycline calcium. *J Drugs Dermatol*. 2013;12:658-663.
90. Lebrun-Vignes B, Kreft-Jais C, Castot A, Chosidow O, French Network of Regional Centers of Pharmacovigilance. Comparative analysis of adverse drug reactions to tetracyclines: results of a French national survey and review of the literature. *Br J Dermatol*. 2012;166:1333-1341.
91. Kermani TA, Ham EK, Camilleri MJ, Warrington KJ. Polyarteritis nodosa-like vasculitis in association with minocycline use: a single-center case series. *Semin Arthritis Rheum*. 2012;42:213-221.
92. Rafiei R, Yaghoobi R. Azithromycin versus tetracycline in the treatment of acne vulgaris. *J Dermatolog Treat*. 2006;17: 217-221.
93. Jen I. A comparison of low dosage trimethoprim/ sulfamethoxazole with oxytetracycline in acne vulgaris. *Cutis*. 1980;26:106-108.
94. Fenner JA, Wiss K, Levin NA. Oral cephalexin for acne vulgaris: clinical experience with 93 patients. *Pediatr Dermatol*. 2008; 25:179-183.
95. Gold LS, Cruz A, Eichenfield L, et al. Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. *Cutis*. 2010;85:94-104.
96. Leyden J, Thiboutot DM, Shalita AR, et al. Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. *Arch Dermatol*. 2006;142:605-612.
97. Margolis DJ, Fanelli M, Hoffstad O, Lewis JD. Potential association between the oral tetracycline class of antimicrobials used to treat acne and inflammatory bowel disease. *Am J Gastroenterol*. 2010;105:2610-2616.
98. Lucky AW, Koltun W, Thiboutot D, et al. A combined oral contraceptive containing 3-mg drospirenone/20-microg ethinyl estradiol in the treatment of acne vulgaris: a randomized, double-blind, placebo-controlled study evaluating lesion counts and participant self-assessment. *Cutis*. 2008;82:143-150.
99. Maloney JM, Dietze P Jr, Watson D, et al. Treatment of acne using a 3-milligram drospirenone/20-microgram ethinyl estradiol oral contraceptive administered in a 24/4 regimen: a randomized controlled trial. *Obstet Gynecol*. 2008;112:773-781.
100. Maloney JM, Dietze P Jr, Watson D, et al. A randomized controlled trial of a low-dose combined oral contraceptive containing 3 mg drospirenone plus 20 microg ethinylestradiol in the treatment of acne vulgaris: lesion counts, investigator ratings and subject self-assessment. *J Drugs Dermatol*. 2009;8:837-844.
101. Plewig G, Cunliffe WJ, Binder N, Hoschen K. Efficacy of an oral contraceptive containing EE 0.03 mg and CMA 2 mg (Belara) in moderate acne resolution: a randomized, double-blind, placebo-controlled phase III trial. *Contraception*. 2009;80: 25-33.
102. Shaw JC. Low-dose adjunctive spironolactone in the treatment of acne in women: a retrospective analysis of 85 consecutively treated patients. *J Am Acad Dermatol*. 2000;43: 498-502.
103. Sato K, Matsumoto D, Iizuka F, et al. Anti-androgenic therapy using oral spironolactone for acne vulgaris in Asians. *Aesthetic Plast Surg*. 2006;30:689-694.
104. Wang HS, Wang TH, Soong YK. Low dose flutamide in the treatment of acne vulgaris in women with or without oligomenorrhea or amenorrhea. *Changgeng Yi Xue Za Zhi*. 1999;22:423-432.
105. Castelo-Branco C, Moyano D, Gomez O, Balasch J. Long-term safety and tolerability of flutamide for the treatment of hirsutism. *Fertil Steril*. 2009;91:1183-1188.
106. Nader S, Rodriguez-Rigau LJ, Smith KD, Steinberger E. Acne and hyperandrogenism: impact of lowering androgen levels with glucocorticoid treatment. *J Am Acad Dermatol*. 1984;11: 256-259.
107. Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. *J Am Acad Dermatol*. 2006;54: 644-646.
108. Goldstein JA, Socha-Szott A, Thomsen RJ, Pochi PE, Shalita AR, Strauss JS. Comparative effect of isotretinoin and etretinate on acne and sebaceous gland secretion. *J Am Acad Dermatol*. 1982;6:760-765.
109. Jones DH, King K, Miller AJ, Cunliffe WJ. A dose-response study of I3-cis-retinoic acid in acne vulgaris. *Br J Dermatol*. 1983;108:333-343.
110. Layton AM, Knaggs H, Taylor J, Cunliffe WJ. Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment. *Br J Dermatol*. 1993;129:292-296.
111. Lehucher-Ceyrac D, Weber-Buisset MJ. Isotretinoin and acne in practice: a prospective analysis of 188 cases over 9 years. *Dermatology*. 1993;186:123-128.
112. Peck GL, Olsen TG, Butkus D, et al. Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. *J Am Acad Dermatol*. 1982;6:735-745.
113. Rubinow DR, Peck GL, Squillace KM, Gantt GG. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. *J Am Acad Dermatol*. 1987;17:25-32.
114. Stainforth JM, Layton AM, Taylor JP, Cunliffe WJ. Isotretinoin for the treatment of acne vulgaris: which factors may predict the need for more than one course? *Br J Dermatol*. 1993;129: 297-301.
115. Strauss JS, Leyden JJ, Lucky AW, et al. A randomized trial of the efficacy of a new micronized formulation versus a

standard formulation of isotretinoin in patients with severe recalcitrant nodular acne. *J Am Acad Dermatol*. 2001;45:187-195.
116. Strauss JS, Rapini RP, Shalita AR, et al. Isotretinoin therapy for acne: results of a multicenter dose-response study. *J Am Acad Dermatol*. 1984;10:490-496.
117. Strauss JS, Stranieri AM. Changes in long-term sebum production from isotretinoin therapy. *J Am Acad Dermatol*. 1982;6:751-756.
118. Goldsmith LA, Bolognia JL, Callen JP, et al. American Academy of Dermatology Consensus Conference on the safe and optimal use of isotretinoin: summary and recommendations. *J Am Acad Dermatol*. 2004;50:900-906.
119. Lehucher-Ceyrac D, de La Salmoniere P, Chastang C, Morel P. Predictive factors for failure of isotretinoin treatment in acne patients: results from a cohort of 237 patients. *Dermatology*. 1999;198:278-283.
120. Strauss JS, Leyden JJ, Lucky AW, et al. Safety of a new micronized formulation of isotretinoin in patients with severe recalcitrant nodular acne: a randomized trial comparing micronized isotretinoin with standard isotretinoin. *J Am Acad Dermatol*. 2001;45:196-207.
121. Webster GF, Leyden JJ, Gross JA. Comparative pharmacokinetic profiles of a novel isotretinoin formulation (isotretinoin-Lidose) and the innovator isotretinoin formulation: a randomized, 4-treatment, crossover study. *J Am Acad Dermatol*. 2013;69:762-767.
122. Alhusayen RO, Juurlink DN, Mamdani MM, Morrow RL, Shear NH, Dormuth CR. Isotretinoin use and the risk of inflammatory bowel disease: a population-based cohort study. *J Invest Dermatol*. 2013;133:907-912.
123. Crockett SD, Gulati A, Sandler RS, Kappelman MD. A causal association between isotretinoin and inflammatory bowel disease has yet to be established. *Am J Gastroenterol*. 2009;104:2387-2393.
124. Crockett SD, Porter CQ, Martin CF, Sandler RS, Kappelman MD. Isotretinoin use and the risk of inflammatory bowel disease: a case-control study. *Am J Gastroenterol*. 2010;105:1986-1993.
125. Etminan M, Bird ST, Delaney JA, Bressler B, Brophy JM. Isotretinoin and risk for inflammatory bowel disease: a nested case-control study and meta-analysis of published and unpublished data. *JAMA Dermatol*. 2013;149:216-220.
126. Reddy D, Siegel CA, Sands BE, Kane S. Possible association between isotretinoin and inflammatory bowel disease. *Am J Gastroenterol*. 2006;101:1569-1573.
127. Sundstrom A, Alfredsson L, Sjolin-Forsberg G, Gerden B, Bergman U, Jokinen J. Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study. *BMJ*. 2010;341:c5812.
128. Bozdag KE, Gulseren S, Guven F, Cam B. Evaluation of depressive symptoms in acne patients treated with isotretinoin. *J Dermatolog Treat*. 2009;20:293-296.
129. Chia CY, Lane W, Chibnall J, Allen A, Siegfried E. Isotretinoin therapy and mood changes in adolescents with moderate to severe acne: a cohort study. *Arch Dermatol*. 2005;141:557-560.
130. Cohen J, Adams S, Patten S. No association found between patients receiving isotretinoin for acne and the development of depression in a Canadian prospective cohort. *Can J Clin Pharmacol*. 2007;14:e227-e233.
131. Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol*. 2000;136:1231-1236.
132. Nevoralova Z, Dvorakova D. Mood changes, depression and suicide risk during isotretinoin treatment: a prospective study. *Int J Dermatol*. 2013;52:163-168.
133. Rehn LM, Meririnne E, Hook-Nikanne J, Isometsa E, Henriksson M. Depressive symptoms and suicidal ideation during isotretinoin treatment: a 12-week follow-up study of male Finnish military conscripts. *J Eur Acad Dermatol Venereol*. 2009;23:1294-1297.
134. Agarwal US, Besarwal RK, Bhola K. Oral isotretinoin in different dose regimens for acne vulgaris: a randomized comparative trial. *Indian J Dermatol Venereol Leprol*. 2011;77:688-694.
135. Akman A, Durusoy C, Senturk M, Koc CK, Soyturk D, Alpsoy E. Treatment of acne with intermittent and conventional isotretinoin: a randomized, controlled multicenter study. *Arch Dermatol Res*. 2007;299:467-473.
136. Borghi A, Mantovani L, Minghetti S, Giari S, Virgili A, Bettoli V. Low-cumulative dose isotretinoin treatment in mild-to-moderate acne: efficacy in achieving stable remission. *J Eur Acad Dermatol Venereol*. 2011;25:1094-1098.
137. Kaymak Y, Ilter N. The effectiveness of intermittent isotretinoin treatment in mild or moderate acne. *J Eur Acad Dermatol Venereol*. 2006;20:1256-1260.
138. Lee JW, Yoo KH, Park KY, et al. Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: a randomized, controlled comparative study. *Br J Dermatol*. 2011;164:1369-1375.
139. Leachman SA, Insogna KL, Katz L, Ellison A, Milstone LM. Bone densities in patients receiving isotretinoin for cystic acne. *Arch Dermatol*. 1999;135:961-965.
140. Bershad S, Rubinstein A, Paterniti JR, et al. Changes in plasma lipids and lipoproteins during isotretinoin therapy for acne. *N Engl J Med*. 1985;313:981-985.
141. De Marchi MA, Maranhao RC, Brandizzi LI, Souza DR. Effects of isotretinoin on the metabolism of triglyceride-rich lipoproteins and on the lipid profile in patients with acne. *Arch Dermatol Res*. 2006;297:403-408.
142. Zech LA, Gross EG, Peck GL, Brewer HB. Changes in plasma cholesterol and triglyceride levels after treatment with oral isotretinoin. A prospective study. *Arch Dermatol*. 1983;119:987-993.
143. Shin J, Cheetham TC, Wong L, et al. The impact of the iPLEDGE program on isotretinoin fetal exposure in an integrated health care system. *J Am Acad Dermatol*. 2011;65:1117-1125.
144. Collins MK, Moreau JF, Opel D, et al. Compliance with pregnancy prevention measures during isotretinoin therapy. *J Am Acad Dermatol*. 2014;70:55-59.
145. Grover C, Reddu BS. The therapeutic value of glycolic acid peels in dermatology. *Indian J Dermatol Venereol Leprol*. 2003;69:148-150.
146. Dreno B, Fischer TC, Perosino E, et al. Expert opinion: efficacy of superficial chemical peels in active acne management—what can we learn from the literature today? Evidence-based recommendations. *J Eur Acad Dermatol Venereol*. 2011;25:695-704.
147. Ilknur T, Demirtasoglu M, Bicak MU, Ozkan S. Glycolic acid peels versus amino fruit acid peels for acne. *J Cosmet Laser Ther*. 2010;12:242-245.
148. Levine RM, Rasmussen JE. Intralesional corticosteroids in the treatment of nodulocystic acne. *Arch Dermatol*. 1983;119:480-481.
149. Potter RA. Intralesional triamcinolone and adrenal suppression in acne vulgaris. *J Invest Dermatol*. 1971;57:364-370.

150. Bassett IB, Pannowitz DL, Barnetson RS. A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne. *Med J Aust*. 1990;153:455-458.
151. Enshaieh S, Jooya A, Siadat AH, Iraji F. The efficacy of 5% topical tea tree oil gel in mild to moderate acne vulgaris: a randomized, double-blind placebo-controlled study. *Indian J Dermatol Venereol Leprol*. 2007;73:22-25.
152. Fouladi RF. Aqueous extract of dried fruit of *Berberis vulgaris L.* in acne vulgaris, a clinical trial. *J Diet Suppl*. 2012; 9:253-261.
153. Hunt MJ, Barnetson RS. A comparative study of gluconolactone versus benzoyl peroxide in the treatment of acne. *Australas J Dermatol*. 1992;33:131-134.
154. Lalla JK, Nandedkar SY, Paranjape MH, Talreja NB. Clinical trials of ayurvedic formulations in the treatment of acne vulgaris. *J Ethnopharmacol*. 2001;78:99-102.
155. Paranjpe P, Kulkarni PH. Comparative efficacy of four Ayurvedic formulations in the treatment of acne vulgaris: a double-blind randomised placebo-controlled clinical evaluation. *J Ethnopharmacol*. 1995;49:127-132.
156. Hughes H, Brown BW, Lawlis GF, Fulton JE Jr. Treatment of acne vulgaris by biofeedback relaxation and cognitive imagery. *J Psychosom Res*. 1983;27:185-191.
157. Smith RN, Mann NJ, Braue A, Makelainen H, Varigos GA. The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. *J Am Acad Dermatol*. 2007;57:247-256.
158. Kwon HH, Yoon JY, Hong JS, Jung JY, Park MS, Suh DH. Clinical and histological effect of a low glycaemic load diet in treatment of acne vulgaris in Korean patients: a randomized, controlled trial. *Acta Derm Venereol*. 2012;92:241-246.
159. Smith R, Mann N, Makelainen H, Roper J, Braue A, Varigos G. A pilot study to determine the short-term effects of a low glycemic load diet on hormonal markers of acne: a nonrandomized, parallel, controlled feeding trial. *Mol Nutr Food Res*. 2008;52:718-726.
160. Preneau S, Dessinioti C, Nguyen JM, Katsambas A, Dreno B. Predictive markers of response to isotretinoin in female acne. *Eur J Dermatol*. 2013;23:478-486.
161. Ismail NH, Manaf ZA, Azizan NZ. High glycemic load diet, milk and ice cream consumption are related to acne vulgaris in Malaysian young adults: a case control study. *BMC Dermatol*. 2012;12:13.
162. Adebamowo CA, Spiegelman D, Berkey CS, et al. Milk consumption and acne in adolescent girls. *Dermatol Online J*. 2006;12:1.
163. Adebamowo CA, Spiegelman D, Berkey CS, et al. Milk consumption and acne in teenaged boys. *J Am Acad Dermatol*. 2008;58:787-793.
164. Di Landro A, Cazzaniga S, Parazzini F, et al. Family history, body mass index, selected dietary factors, menstrual history, and risk of moderate to severe acne in adolescents and young adults. *J Am Acad Dermatol*. 2012;67: 1129-1135.
165. Seirafi H, Farnaghi F, Vasheghani-Farahani A, et al. Assessment of androgens in women with adult-onset acne. *Int J Dermatol*. 2007;46:1188-1191.
166. Degitz K, Placzek M, Arnold B, Schmidt H, Plewig G. Congenital adrenal hyperplasia and acne in male patients. *Br J Dermatol*. 2003;148:1263-1266.
167. Trapp CM, Oberfield SE. Recommendations for treatment of nonclassic congenital adrenal hyperplasia (NCCAH): an update. *Steroids*. 2012;77:342-346.
168. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2013;98:4565-4592.
169. Saleh BO. Role of growth hormone and insulin-like growth factor-I in hyperandrogenism and the severity of acne vulgaris in young males. *Saudi Med J*. 2012;33:1196-1200.
170. Del Prete M, Mauriello MC, Faggiano A, et al. Insulin resistance and acne: a new risk factor for men? *Endocrine*. 2012;42:555-560.
171. Cunliffe WJ, Dodman B, Ead R. Benzoyl peroxide in acne. *Practitioner*. 1978;220:479-482.
172. Fulton JE Jr, Farzad-Bakshandeh A, Bradley S. Studies on the mechanism of action to topical benzoyl peroxide and vitamin A acid in acne vulgaris. *J Cutan Pathol*. 1974;1:191-200.
173. Padilla RS, McCabe JM, Becker LE. Topical tetracycline hydrochloride vs. topical clindamycin phosphate in the treatment of acne: a comparative study. *Int J Dermatol*. 1981;20:445-448.
174. Pariser DM, Rich P, Cook-Bolden FE, Korotzer A. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 3.75% for the once-daily treatment of moderate to severe acne vulgaris. *J Drugs Dermatol*. 2014;13: 1083-1089.
175. Lucky AW, Cullen SI, Funicella T, et al. Double-blind, vehicle-controlled, multicenter comparison of two 0.025% tretinoin creams in patients with acne vulgaris. *J Am Acad Dermatol*. 1998;38:S24-S30.
176. Dreno B, Bettoli V, Ochsendorf F, et al. Efficacy and safety of clindamycin phosphate 1.2%/tretinoin 0.025% formulation for the treatment of acne vulgaris: pooled analysis of data from three randomised, double-blind, parallel-group, phase III studies. *Eur J Dermatol*. 2014;24:201-209.
177. Pedace FJ, Stoughton R. Topical retinoic acid in acne vulgaris. *Br J Dermatol*. 1971;84:465-469.
178. Kircik LH. Efficacy and safety of azelaic acid (AzA) gel 15% in the treatment of post-inflammatory hyperpigmentation and acne: a 16-week, baseline-controlled study. *J Drugs Dermatol*. 2011;10:586-590.
179. Del Rosso JQ, Kircik L, Gallagher CJ. Comparative efficacy and tolerability of dapsone 5% gel in adult versus adolescent females with acne vulgaris. *J Clin Aesthet Dermatol*. 2015;8: 31-37.
180. Shalita AR. Comparison of a salicylic acid cleanser and a benzoyl peroxide wash in the treatment of acne vulgaris. *Clin Ther*. 1989;11:264-267.
181. Elstein W. Topical deodorized polysulfides. Broadscope acne therapy. *Cutis*. 1981;28:468-472.
182. Hurley HJ, Shelley WB. Special topical approach to the treatment of acne. Suppression of sweating with aluminum chloride in an anhydrous formulation. *Cutis*. 1978;22:696-703.
183. Hjorth N, Storm D, Dela K. Topical anhydrous aluminum chloride formulation in the treatment of acne vulgaris: a double-blind study. *Cutis*. 1985;35:499-500.
184. Bojar RA, Eady EA, Jones CE, Cunliffe WJ, Holland KT. Inhibition of erythromycin-resistant propionibacteria on the skin of acne patients by topical erythromycin with and without zinc. *Br J Dermatol*. 1994;130:329-336.
185. Cochran RJ, Tucker SB, Flannigan SA. Topical zinc therapy for acne vulgaris. *Int J Dermatol*. 1985;24:188-190.
186. Stainforth J, MacDonald-Hull S, Papworth-Smith JW, Eady EA, Cunliffe WJ, Norris JFB. A single-blind comparison of topical erythromycin/zinc lotion and oral minocycline in the treatment of acne vulgaris. *J Dermatolog Treat*. 1993;4: 119-122.

187. Lebrun CM. Rosac cream with sunscreens (sodium sulfacetamide 10% and sulfur 5%). *Skinmed*. 2004;3:92.
188. Tarimci N, Sener S, Kilinc T. Topical sodium sulfacetamide/sulfur lotion. *J Clin Pharm Ther*. 1997;22:301.
189. Thiboutot D. New treatments and therapeutic strategies for acne. *Arch Fam Med*. 2000;9:179-187.
190. Shalita AR, Smith JG, Parish LC, Sofman MS, Chalker DK. Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol*. 1995;34:434-437.
191. Khodaeiani E, Fouladi RF, Amirnia M, Saeidi M, Karimi ER. Topical 4% nicotinamide vs. 1% clindamycin in moderate inflammatory acne vulgaris. *Int J Dermatol*. 2013;52:999-1004.
192. Tan J, Humphrey S, Vender R, et al. A treatment for severe nodular acne: a randomized investigator-blinded, controlled, noninferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs. oral isotretinoin. *Br J Dermatol*. 2014;171:1508-1516.
193. Zaenglein AL, Shamban A, Webster G, et al. A phase IV, open-label study evaluating the use of triple-combination therapy with minocycline HCl extended-release tablets, a topical antibiotic/retinoid preparation and benzoyl peroxide in patients with moderate to severe acne vulgaris. *J Drugs Dermatol*. 2013;12:619-625.
194. Fleischer AB Jr, Dinehart S, Stough D, et al. Safety and efficacy of a new extended-release formulation of minocycline. *Cutis*. 2006;78:21-31.
195. Toossi P, Farshchian M, Malekzad F, Mohtasham N, Kimyai-Asadi A. Subantimicrobial-dose doxycycline in the treatment of moderate facial acne. *J Drugs Dermatol*. 2008;7:1149-1152.
196. Moore A, Ling M, Bucko A, Manna V, Rueda MJ. Efficacy and safety of subantimicrobial dose, modified-release doxycycline 40 mg versus doxycycline 100 mg versus placebo for the treatment of inflammatory lesions in moderate and severe acne: a randomized, double-blinded, controlled study. *J Drugs Dermatol*. 2015;14:581-586.
197. Maleszka R, Turek-Urasinska K, Oremus M, Vukovic J, Barsic B. Pulsed azithromycin treatment is as effective and safe as 2-week-longer daily doxycycline treatment of acne vulgaris: a randomized, double-blind, noninferiority study. *Skinmed*. 2011;9:86-94.
198. Antonio JR, Pegas JR, Cestari TF, Do Nascimento LV. Azithromycin pulses in the treatment of inflammatory and pustular acne: efficacy, tolerability and safety. *J Dermatolog Treat*. 2008;19:210-215.
199. Innocenzi D, Skroza N, Ruggiero A, et al. Moderate acne vulgaris: efficacy, tolerance and compliance of oral azithromycin thrice weekly for. *Acta Dermatovenerol Croat*. 2008;16:13-18.
200. Bardazzi F, Savoia F, Parente G, et al. Azithromycin: a new therapeutical strategy for acne in adolescents. *Dermatol Online J*. 2007;13:4.
201. Basta-Juzbasic A, Lipozencic J, Oremovic L, et al. A dose-finding study of azithromycin in the treatment of acne vulgaris. *Acta Dermatovenerol Croat*. 2007;15:141-147.
202. Kus S, Yucelten D, Aytug A. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of acne vulgaris. *Clin Exp Dermatol*. 2005;30:215-220.
203. Parsad D, Pandhi R, Nagpal R, Negi KS. Azithromycin monthly pulse vs daily doxycycline in the treatment of acne vulgaris. *J Dermatol*. 2001;28:1-4.
204. Gruber F, Grubisic-Greblo H, Kastelan M, et al. Azithromycin compared with minocycline in the treatment of acne comedonica and papulo-pustulosa. *J Chemother*. 1998;10:469-473.
205. Ullah G, Noor SM, Bhatti Z, Ahmad M, Bangash AR. Comparison of oral azithromycin with oral doxycycline in the treatment of acne vulgaris. *J Ayub Med Coll Abbottabad*. 2014;26:64-67.
206. Shaughnessy KK, Bouchard SM, Mohr MR, Herre JM, Salkey KS. Minocycline-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with persistent myocarditis. *J Am Acad Dermatol*. 2010;62:315-318.
207. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. *Clin Ther*. 2005;27:1329-1342.
208. Tripathi SV, Gustafson CJ, Huang KE, Feldman SR. Side effects of common acne treatments. *Exp Opin Drug Saf*. 2013;12:39-51.
209. Weinstein M, Laxer R, Debosz J, Somers G. Doxycycline-induced cutaneous inflammation with systemic symptoms in a patient with acne vulgaris. *J Cutan Med Surg*. 2013;17:283-286.
210. Firoz BF, Henning JS, Zarzabal LA, Pollock BH. Toxic epidermal necrolysis: five years of treatment experience from a burn unit. *J Am Acad Dermatol*. 2012;67:630-635.
211. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med*. 1995;333:1600-1607.
212. Thiboutot DM, Shalita AR, Yamauchi PS, et al. Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris: a randomized, controlled, investigator-blind follow-up of a recent combination study. *Arch Dermatol*. 2006;142:597-602.
213. Poulin Y, Sanchez NP, Bucko A, et al. A 6-month maintenance therapy with adapalene-benzoyl peroxide gel prevents relapse and continuously improves efficacy among patients with severe acne vulgaris: results of a randomized controlled trial. *Br J Dermatol*. 2011;164:1376-1382.
214. Tan J, Stein Gold L, Schlessinger J, et al. Short-term combination therapy and long-term relapse prevention in the treatment of severe acne vulgaris. *J Drugs Dermatol*. 2012;11:174-180.
215. Moon SH, Roh HS, Kim YH, et al. Antibiotic resistance of microbial strains isolated from Korean acne patients. *J Dermatol*. 2012;39:833-837.
216. Margolis DJ, Fanelli M, Kupperman E, et al. Association of pharyngitis with oral antibiotic use for the treatment of acne: a cross-sectional and prospective cohort study. *Arch Dermatol*. 2012;148:326-332.
217. Bartlett JG, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. *N Engl J Med*. 1978;298:531-534.
218. Carroll KC, Bartlett JG. Biology of *Clostridium difficile*: implications for epidemiology and diagnosis. *Annu Rev Microbiol*. 2011;65:501-521.
219. Arrington EA, Patel NS, Gerancher K, Feldman SR. Combined oral contraceptives for the treatment of acne: a practical guide. *Cutis*. 2012;90:83-90.
220. Davtyan C. Four generations of progestins in oral contraceptives. *Proceedings of UCLA Healthcare*. 2012;16. Available at: www.med.ucla.edu/modules/xfsection/download.php?fileid=638. Accessed January 5, 2016.
221. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. *Cochrane Database Syst Rev*. 2012;(6):CD004425.

222. Harper JC. Should dermatologists prescribe hormonal contraceptives for acne? *Dermatol Ther*. 2009;22:452-457.
223. Rabe T, Kowald A, Ortmann J, Rehberger-Schneider S. Inhibition of skin 5 alpha-reductase by oral contraceptive progestins in vitro. *Gynecol Endocrinol*. 2000;14:223-230.
224. Koltun W, Lucky AW, Thiboutot D, et al. Efficacy and safety of 3 mg drospirenone/20 mcg ethinylestradiol oral contraceptive administered in 24/4 regimen in the treatment of acne vulgaris: a randomized, double-blind, placebo-controlled trial. *Contraception*. 2008;77:249-256.
225. Koltun W, Maloney JM, Marr J, Kunz M. Treatment of moderate acne vulgaris using a combined oral contraceptive containing ethinylestradiol 20 mug plus drospirenone 3 mg administered in a 24/4 regimen: a pooled analysis. *Eur J Obstet Gynecol Reprod Biol*. 2011;155:171-175.
226. Jaisamrarn U, Chaovisitsaree S, Angsuwathana S, Nerapusee O. A comparison of multiphasic oral contraceptives containing norgestimate or desogestrel in acne treatment: a randomized trial. *Contraception*. 2014;90:535-541.
227. Palli MB, Reyes-Habito CM, Lima XT, Kimball AB. A single-center, randomized double-blind, parallel-group study to examine the safety and efficacy of 3mg drospirenone/0.02 mg ethinyl estradiol compared with placebo in the treatment of moderate truncal acne vulgaris. *J Drugs Dermatol*. 2013;12:633-637.
228. George R, Clarke S, Thiboutot D. Hormonal therapy for acne. *Semin Cutan Med Surg*. 2008;27:188-196.
229. The American College of Obstetricians and Gynecologists website. Committee opinion 540. Risk of venous thromboembolism among users of drospirenone-containing oral contraceptive pills. Available at: http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/Risk-of-Venous-Thromboembolism. Accessed January 6, 2016.
230. US Food and Drug Administration website. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf. Accessed January 6, 2016.
231. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet*. 1997;349:1202-1209.
232. Katsambas AD, Dessinioti C. Hormonal therapy for acne: why not as first line therapy? facts and controversies. *Clin Dermatol*. 2010;28:17-23.
233. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 1997;350:1047-1059.
234. Gierisch JM, Coeytaux RR, Urrutia RP, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. *Cancer Epidemiol Biomarkers Prev*. 2013;22:1931-1943.
235. International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral V, Berrington de González A, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet*. 2007;370:1609-1621.
236. Lloyd T, Rollings N, Andon MB, et al. Determinants of bone density in young women. I. Relationships among pubertal development, total body bone mass, and total body bone density in premenarchal females. *J Clin Endocrinol Metab*. 1992;75:383-387.
237. Cromer BA, Bonny AE, Stager M, et al. Bone mineral density in adolescent females using injectable or oral contraceptives: a 24-month prospective study. *Fertil Steril*. 2008;90:2060-2067.
238. Lloyd T, Petit MA, Lin HM, Beck TJ. Lifestyle factors and the development of bone mass and bone strength in young women. *J Pediatr*. 2004;144:776-782.
239. Maguire K, Westhoff C. The state of hormonal contraception today: established and emerging noncontraceptive health benefits. *Am J Obstet Gynecol*. 2011;205(4 suppl):S4-S8.
240. ACOG Committee on Practice Bulletins-Gynecology. ACOG practice bulletin. No. 73: Use of hormonal contraception in women with coexisting medical conditions. *Obstet Gynecol*. 2006;107:1453-1472.
241. Helms SE, Bredle DL, Zajic J, Jarjoura D, Brodell RT, Krishnarao I. Oral contraceptive failure rates and oral antibiotics. *J Am Acad Dermatol*. 1997;36:705-710.
242. London BM, Lookingbill DP. Frequency of pregnancy in acne patients taking oral antibiotics and oral contraceptives. *Arch Dermatol*. 1994;130:392-393.
243. Krunic A, Ciurea A, Scheman A. Efficacy and tolerance of acne treatment using both spironolactone and a combined contraceptive containing drospirenone. *J Am Acad Dermatol*. 2008;58:60-62.
244. Stewart FH, Harper CC, Ellertson CE, Grimes DA, Sawaya GF, Trussell J. Clinical breast and pelvic examination requirements for hormonal contraception: current practice vs evidence. *JAMA*. 2001;285:2232-2239.
245. Cusan L, Dupont A, Gomez JL, Tremblay RR, Labrie F. Comparison of flutamide and spironolactone in the treatment of hirsutism: a randomized controlled trial. *Fertil Steril*. 1994;61:281-287.
246. Boisselle A, Dionne FT, Tremblay RR. Interaction of spironolactone with rat skin androgen receptor. *Can J Biochem*. 1979;57:1042-1046.
247. Menard RH, Martin HF, Stripp B, Gillette JR, Bartter FC. Spironolactone and cytochrome P-450: impairment of steroid hydroxylation in the adrenal cortex. *Life Sci*. 1974;15:1639-1648.
248. Menard RH, Stripp B, Gillette JR. Spironolactone and testicular cytochrome P-450: decreased testosterone formation in several species and changes in hepatic drug metabolism. *Endocrinology*. 1974;94:1628-1636.
249. Rifka SM, Pita JC, Vigersky RA, Wilson YA, Loriaux DL. Interaction of digitalis and spironolactone with human sex steroid receptors. *J Clin Endocrinol Metab*. 1978;46:338-344.
250. Zouboulis CC, Akamatsu H, Stephanek K, Orfanos CE. Androgens affect the activity of human sebocytes in culture in a manner dependent on the localization of the sebaceous glands and their effect is antagonized by spironolactone. *Skin Pharmacol*. 1994;7:33-40.
251. Serafini PC, Catalino J, Lobo RA. The effect of spironolactone on genital skin 5 alpha-reductase activity. *J Steroid Biochem*. 1985;23:191-194.
252. Muhlemann MF, Carter GD, Cream JJ, Wise P. Oral spironolactone: an effective treatment for acne vulgaris in women. *Br J Dermatol*. 1986;115:227-232.
253. Goodfellow A, Alaghband-Zadeh J, Carter G, et al. Oral spironolactone improves acne vulgaris and reduces sebum excretion. *Br J Dermatol*. 1984;111:209-214.
254. Brown J, Farquhar C, Lee O, Toomath R, Jepson RG. Spironolactone versus placebo or in combination with

steroids for hirsutism and/or acne. *Cochrane Database Syst Rev*. 2009;(2):CD000194.
255. Shaw JC, White LE. Long-term safety of spironolactone in acne: results of an 8-year followup study. *J Cutan Med Surg*. 2002;6:541-545.
256. Plovanich M, Weng QY, Mostaghimi A. Low usefulness of potassium monitoring among healthy young women taking spironolactone for acne. *JAMA Dermatol*. 2015;151:941-944.
257. Zeichner JA. Evaluating and treating the adult female patient with acne. *J Drugs Dermatol*. 2013;12:1416-1427.
258. Loube SD, Quirk RA. Letter: breast cancer associated with administration of spironolactone. *Lancet*. 1975;1:1428-1429.
259. Danielson DA, Jick H, Hunter JR, Stergachis A, Madsen S. Nonestrogenic drugs and breast cancer. *Am J Epidemiol*. 1982;116:329-332.
260. Friedman GD, Ury HK. Initial screening for carcinogenicity of commonly used drugs. *J Natl Cancer Inst*. 1980;65:723-733.
261. Mackenzie IS, Macdonald TM, Thompson A, Morant S, Wei L. Spironolactone and risk of incident breast cancer in women older than 55 years: retrospective, matched cohort study. *BMJ*. 2012;345:e4447.
262. Biggar RJ, Andersen EW, Wohlfahrt J, Melbye M. Spironolactone use and the risk of breast and gynecologic cancers. *Cancer Epidemiol*. 2013;37:870-875.
263. Cusan L, Dupont A, Belanger A, Tremblay RR, Manhes G, Labrie F. Treatment of hirsutism with the pure antiandrogen flutamide. *J Am Acad Dermatol*. 1990;23:462-469.
264. Muderris II, Bayram F, Guven M. Treatment of hirsutism with lowest-dose flutamide (62.5 mg/day). *Gynecol Endocrinol*. 2000;14:38-41.
265. Carmina E, Lobo RA. A comparison of the relative efficacy of antiandrogens for the treatment of acne in hyperandrogenic women. *Clin Endocrinol*. 2002;57:231-234.
266. Adalatkhah H, Pourfarzi F, Sadeghi-Bazargani H. Flutamide versus a cyproterone acetate-ethinyl estradiol combination in moderate acne: a pilot randomized clinical trial. *Clin Cosmet Investig Dermatol*. 2011;4:117-121.
267. Calaf J, Lopez E, Millet A, et al. Long-term efficacy and tolerability of flutamide combined with oral contraception in moderate to severe hirsutism: a 12-month, double-blind, parallel clinical trial. *J Clin Endocrinol Metab*. 2007;92:3446-3452.
268. Wysowski DK, Freiman JP, Tourtelot JB, Horton ML 3rd. Fatal and nonfatal hepatotoxicity associated with flutamide. *Ann Intern Med*. 1993;118:860-864.
269. Garcia Cortes M, Andrade RJ, Lucena MI, et al. Flutamide-induced hepatotoxicity: report of a case series. *Rev Esp Enferm Dig*. 2001;93:423-432.
270. Saihan EM, Burton JL. Sebaceous gland suppression in female acne patients by combined glucocorticoid-oestrogen therapy. *Br J Dermatol*. 1980;103:139-142.
271. Darley CR, Moore JW, Besser GM, Munro DD, Kirby JD. Low dose prednisolone or oestrogen in the treatment of women with late onset or persistent acne vulgaris. *Br J Dermatol*. 1982;108:345-353.
272. Jansen T, Plewig G. Acne fulminans. *Int J Dermatol*. 1998;37:254-257.
273. Karvonen SL. Acne fulminans: report of clinical findings and treatment of twenty-four patients. *J Am Acad Dermatol*. 1993;28:572-579.
274. Chivot M, Midoun H. Isotretinoin and acne—a study of relapses. *Dermatologica*. 1990;180:240-243.
275. Goulden V, Clark SM, McGeown C, Cunliffe WJ. Treatment of acne with intermittent isotretinoin. *Br J Dermatol*. 1997;137:106-108.
276. King K, Jones DH, Daltrey DC, Cunliffe WJ. A double-blind study of the effects of 13-cis-retinoic acid on acne, sebum excretion rate and microbial population. *Br J Dermatol*. 1982;107:583-590.
277. Lester RS, Schachter GD, Light MJ. Isotretinoin and tetracycline in the management of severe nodulocystic acne. *Int J Dermatol*. 1985;24:252-257.
278. Blasiak RC, Stamey CR, Burkhart CN, Lugo-Somolinos A, Morrell DS. High-dose isotretinoin treatment and the rate of retrial, relapse, and adverse effects in patients with acne vulgaris. *JAMA Dermatol*. 2013;149:1392-1398.
279. De D, Kanwar AJ. Combination of low-dose isotretinoin and pulsed oral azithromycin in the management of moderate to severe acne: a preliminary open-label, prospective, non-comparative, single-centre study. *Clin Drug Investig*. 2011;31:599-604.
280. Lee JJ, Feng L, Reshef DS, et al. Mortality in the randomized, controlled lung intergroup trial of isotretinoin. *Cancer Prev Res (Phila)*. 2010;3:738-744.
281. Bernstein CN, Nugent Z, Longobardi T, Blanchard JF. Isotretinoin is not associated with inflammatory bowel disease: a population-based case-control study. *Am J Gastroenterol*. 2009;104:2774-2778.
282. Dubeau MF, Iacucci M, Beck PL, et al. Drug-induced inflammatory bowel disease and IBD-like conditions. *Inflamm Bowel Dis*. 2013;19:445-456.
283. Rashtak S, Khaleghi S, Pittelkow MR, Larson JJ, Lahr BD, Murray JA. Isotretinoin exposure and risk of inflammatory bowel disease. *JAMA Dermatol*. 2014;150:1322-1326.
284. American Academy of Dermatology website. Position statement on isotretinoin. Available at: https://www.aad.org/Forms/Policies/Uploads/PS/PS-Isotretinoin.pdf. Accessed January 6, 2016.
285. Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. *Semin Cutan Med Surg*. 2005;24:92-102.
286. Hull SM, Cunliffe WJ, Hughes BR. Treatment of the depressed and dysmorphophobic acne patient. *Clin Exp Dermatol*. 1991;16:210-211.
287. Myhill JE, Leichtman SR, Burnett JW. Self-esteem and social assertiveness in patients receiving isotretinoin treatment for cystic acne. *Cutis*. 1988;41:171-173.
288. Ormerod AD, Thind CK, Rice SA, Reid IC, Williams JH, McCaffery PJ. Influence of isotretinoin on hippocampal-based learning in human subjects. *Psychopharmacology*. 2012;221:667-674.
289. Luthi F, Eggel Y, Theumann N. Premature epiphyseal closure in an adolescent treated by retinoids for acne: an unusual cause of anterior knee pain. *Joint Bone Spine*. 2012;79:314-316.
290. Steele RG, Lugg P, Richardson M. Premature epiphyseal closure secondary to single-course vitamin A therapy. *Aust N Z J Surg*. 1999;69:825-827.
291. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. *N Engl J Med*. 1985;313:837-841.
292. McElwee NE, Schumacher MC, Johnson SC, et al. An observational study of isotretinoin recipients treated for acne in a health maintenance organization. *Arch Dermatol*. 1991;127:341-346.
293. Rubenstein R, Roenigk HH Jr, Stegman SJ, Hanke CW. Atypical keloids after dermabrasion of patients taking isotretinoin. *J Am Acad Dermatol*. 1986;15:280-285.
294. Zachariae H. Delayed wound healing and keloid formation following argon laser treatment or dermabrasion during isotretinoin treatment. *Br J Dermatol*. 1988;118:703-706.

295. Bagatin E, Parada MO, Miot HA, Hassun KM, Michalany N, Talarico S. A randomized and controlled trial about the use of oral isotretinoin for photoaging. *Int J Dermatol*. 2010;49: 207-214.
296. Picosse FR, Yarak S, Cabral NC, Bagatin E. Early chemabrasion for acne scars after treatment with oral isotretinoin. *Dermatol Surg*. 2012;38:1521-1526.
297. Chandrashekar BS, Varsha DV, Vasanth V, Jagadish P, Madura C, Rajashekar ML. Safety of performing invasive acne scar treatment and laser hair removal in patients on oral isotretinoin: a retrospective study of 110 patients. *Int J Dermatol*. 2014;53:1281-1285.
298. Kim HW, Chang SE, Kim JE, Ko JY, Ro YS. The safe delivery of fractional ablative carbon dioxide laser treatment for acne scars in Asian patients receiving oral isotretinoin. *Dermatol Surg*. 2014;40:1361-1366.
299. Yoon JH, Park EJ, Kwon IH, et al. Concomitant use of an infrared fractional laser with low-dose isotretinoin for the treatment of acne and acne scars. *J Dermatolog Treat*. 2014; 25:142-146.
300. Basak PY, Cetin ES, Gurses I, Ozseven AG. The effects of systemic isotretinoin and antibiotic therapy on the microbial floras in patients with acne vulgaris. *J Eur Acad Dermatol Venereol*. 2013;27:332-336.
301. Williams RE, Doherty VR, Perkins W, Aitchison TC, Mackie RM. Staphylococcus aureus and intra-nasal mupirocin in patients receiving isotretinoin for acne. *Br J Dermatol*. 1992;126: 362-366.
302. Dai WS, LaBraico JM, Stern RS. Epidemiology of isotretinoin exposure during pregnancy. *J Am Acad Dermatol*. 1992;26: 599-606.
303. Atzori L, Brundu MA, Orru A, Biggio P. Glycolic acid peeling in the treatment of acne. *J Eur Acad Dermatol Venereol*. 1999;12: 119-122.
304. Levesque A, Hamzavi I, Seite S, Rougier A, Bissonnette R. Randomized trial comparing a chemical peel containing a lipophilic hydroxy acid derivative of salicylic acid with a salicylic acid peel in subjects with comedonal acne. *J Cosmet Dermatol*. 2011;10:174-178.
305. Pollock B, Turner D, Stringer MR, et al. Topical amino-laevulinic acid-photodynamic therapy for the treatment of acne vulgaris: a study of clinical efficacy and mechanism of action. *Br J Dermatol*. 2004;151:616-622.
306. Gold MH, Bradshaw VL, Boring MM, Bridges TM, Biron JA, Carter LN. The use of a novel intense pulsed light and heat source and ALA-PDT in the treatment of moderate to severe inflammatory acne vulgaris. *J Drugs Dermatol*. 2004;3(6 suppl):S15-S19.
307. Wang XL, Wang HW, Zhang LL, Guo MX, Huang Z. Topical ALA PDT for the treatment of severe acne vulgaris. *Photodiagnosis Photodyn Ther*. 2010;7:33-38.
308. Ma L, Xiang LH, Yu B, et al. Low-dose topical 5-aminolevulinic acid photodynamic therapy in the treatment of different severity of acne vulgaris. *Photodiagnosis Photodyn Ther*. 2013; 10:583-590.
309. Lee SJ, Hyun MY, Park KY, Kim BJ. A tip for performing intralesional triamcinolone acetonide injections in acne patients. *J Am Acad Dermatol*. 2014;71:e127-e128.
310. Kim KS, Kim YB. Anti-inflammatory effect of Keigai-rengyo-to extract and acupuncture in male patients with acne vulgaris: a randomized controlled pilot trial. *J Altern Complement Med*. 2012;18:501-508.
311. Burris J, Rietkerk W, Woolf K. Relationships of self-reported dietary factors and perceived acne severity in a cohort of New York young adults. *J Acad Nutr Diet*. 2014;114: 384-392.
312. Adebamowo CA, Spiegelman D, Danby FW, Frazier AL, Willett WC, Holmes MD. High school dietary dairy intake and teenage acne. *J Am Acad Dermatol*. 2005;52: 207-214.
313. Sardana K, Garg VK. An observational study of methionine-bound zinc with antioxidants for mild to moderate acne vulgaris. *Derm Ther*. 2010;23:411-418.
314. Jung GW, Tse JE, Guiha I, Rao J. Prospective, randomized, open-label trial comparing the safety, efficacy, and tolerability of an acne treatment regimen with and without a probiotic supplement and minocycline in subjects with mild to moderate acne. *J Cutan Med Surg*. 2013;17: 114-122.
315. Khayef G, Young J, Burns-Whitmore B, Spalding T. Effects of fish oil supplementation on inflammatory acne. *Lipids Health Dis*. 2012;11:165.

Supplemental Table I. Prescribing information for benzoyl peroxide

Indication	Topical treatment of mild to moderate acne vulgaris
Dosing	2.5%, 5%, or 10% in gel, wash, or cream
Duration of dosing	Continuing use of the drug is normally required to maintain a satisfactory clinical response
Contraindications	Should not be used in patients who have shown hypersensitivity to benzoyl peroxide or to any of the other ingredients in the products
Efficacy	Clinically visible improvements will normally occur by the third week of therapy. Maximum lesion reduction may be expected after approximately 8 to 12 weeks of drug use
Adverse effects/toxicities	Hypersensitivity reactions, contact sensitization reactions, excessive erythema, and peeling
Pregnancy category	C
Nursing	It is not known whether this drug is excreted in human milk
Pediatric use	Safety and effectiveness have not been established in children <12 years of age

Supplemental Table II. Prescribing information for salicylic acid

Indication	Salicylic acid is used alone or in combination with other drugs for the symptomatic treatment of acne
Dosing	Apply topically using appropriate preparations containing salicylic acid 0.5-2%
Duration of dosing	Apply appropriate 0.5-2% salicylic acid preparation 1-3 times daily. Initially, apply once daily then gradually increase to 2 or 3 times daily, if necessary. If dryness or peeling occurs, reduce application to once daily or every other day
Contraindications	Known sensitivity to salicylic acid or any other ingredient in the formulation
Adverse effects/toxicities	Hypersensitivity reactions, salicylate toxicity, excessive erythema, and scaling
Interactions	Acidifying agents, anticoagulants, antidiabetic agents, aspirin, corticosteroids, diuretics, methotrexate, pyrazinamide, sulfur, and uricosuric agents
Other issues	Cumulative irritant or drying effect. If excessive dryness occurs, use only 1 topical medication unless directed by a clinician
Pregnancy category	C
Nursing	Discontinue nursing or the drug. If used by nursing women, avoid applying to the chest area
Pediatric use	Salicylic acid 6% cream, lotion, and gel and 15% plaster not recommended in children <2 years of age. Increased risk of salicylate toxicity with prolonged, excessive use in children <12 years of age. Limit treatment area and monitor for possible signs of salicylate toxicity. Use of salicylates in children with varicella infection or influenza-like illnesses is associated with an increased risk of developing Reye syndrome

Supplemental Table III. Prescribing information for erythromycin (topical)

Indication	Topical treatment of acne vulgaris
Dosing	Apply 2% solution, ointment, pledget, or gel as a thin film to affected area once or twice daily
Duration of dosing	Maintenance therapy needed to prevent recurrence
Contraindications	Known hypersensitivity to erythromycin or any ingredient in the formulation
Efficacy	Generally effective for the treatment of mild to moderate inflammatory acne. Main action is prevention of new lesions
Other results	May induce bacterial resistance when used as monotherapy; resistance associated with decreased clinical efficacy
Adverse effects/toxicities	Superinfection/*Clostridium difficile*—associated colitis
Interactions	Alcohol-containing cosmetics; medicated soaps or abrasive, peeling, or desquamating agents; clindamycin, sulfur, and tretinoin
Other issues	Cumulative irritant or drying effect
Pregnancy category	B
Nursing	Caution if used in nursing women. Not known whether erythromycin is distributed into milk after topical application
Pediatric use	Safety and efficacy of single-entity topical gel or solution not established in children

Supplemental Table IV. Prescribing information for combination erythromycin and benzoyl peroxide

Indication	Topical treatment of acne vulgaris
Dosing	Applied twice daily, morning and evening, after the skin is thoroughly washed, rinsed with warm water, and gently patted dry
Contraindications	Individuals who have shown hypersensitivity to any components of formulation. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents
Efficacy	In 2 controlled clinical studies, the combination of erythromycin and benzoyl peroxide applied twice daily for 8 weeks was significantly more effective than vehicle
Adverse effects/toxicities	Pseudomembranous colitis, dryness, urticarial reaction, peeling, itching, burning sensation, erythema, inflammation of the face/eyes/nose, skin discoloration, oiliness, and tenderness of skin
Other issues	Cumulative irritant or drying effect; use with caution
Pregnancy category	C
Nursing	Caution if used in nursing women. It is not known whether erythromycin or benzoyl peroxide is distributed into milk after topical application
Pediatric use	Safety and effectiveness have not been established in pediatric patients $<$12 years of age

Supplemental Table V. Prescribing information for clindamycin

Indication	Topical application in the treatment of acne vulgaris
Dosing	Apply a thin film of clindamycin once daily to the skin where acne lesions appear. Use enough to cover the entire affected area lightly
Contraindications	History of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic associated colitis
Efficacy	In a 12-week controlled clinical trial, 1% topical clindamycin gel applied once daily was more effective than the vehicle applied once daily
Adverse effects/toxicities	Severe colitis, dermatitis, folliculitis, photosensitivity reaction, pruritus, erythema, dry skin, and peeling
Interactions	Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents
Pregnancy category	B
Nursing	It is not known whether clindamycin is excreted in human milk
Pediatric use	Safety and effectiveness have not been established in children <12 years of age

Supplemental Table VI. Prescribing information for combination clindamycin + benzoyl peroxide

Indication	Topical treatment of inflammatory acne vulgaris
Dosing	Apply a thin layer to the face once daily, in the evening
Contraindications	Patients who have had hypersensitivity (eg, anaphylaxis) to clindamycin, benzoyl peroxide, any components of the formulation, or lincomycin. Patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis (including pseudomembranous colitis)
Efficacy	Combined clindamycin plus benzoyl peroxide topically applied once daily for 11 weeks was significantly more effective than vehicle, benzoyl peroxide, and clindamycin in the treatment of inflammatory lesions of moderate to moderately severe facial acne vulgaris in 3 of 5 trials
Other results	Has not been shown to have any additional benefit when compared with benzoyl peroxide alone in the same vehicle when used for the treatment of noninflammatory acne
Adverse effects/toxicities	Erythema, peeling, dryness, burning, and anaphylaxis
Interactions	Should not be used in combination with erythromycin-containing products, with concomitant topical medications, or with neuromuscular blocking agents
Other issues	Ultraviolet light and environmental exposure (including use of tanning beds or sun lamps). Minimize sun exposure after drug application
Pregnancy category	C
Nursing	It is not known whether clindamycin or benzoyl peroxide is excreted into human milk after topical application
Pediatric use	Safety and effectiveness of combination clindamycin and benzoyl peroxide have not been established in pediatric patients $<$12 years of age

Supplemental Table VII. Prescribing information for tretinoin

Indication	Topical treatment of acne vulgaris
Dosing	Apply a thin layer of tretinoin once daily, before bedtime, to skin where lesions occur. Keep away from eyes, mouth, nasal creases, and mucous membranes
Contraindications	Known hypersensitivity to tretinoin or any ingredient in the formulation
Efficacy	In controlled trials, 21-23% of patients using topical tretinoin had successful treatment (using 6-point global severity score)
Adverse effects/toxicities	Dry skin, peeling, scaling, flaking, burning sensation, erythema, pruritus, pain of skin, sunburn, and hyper-/hypopigmentation
Interactions	Keratolytic agents and photosensitizing agents
Other issues	Ultraviolet light and environmental exposures (eg, wind and cold) can cause irritation and should be avoided; cautions should be used in patients with fish allergies (for specific formulation of tretinoin 0.05%)
Pregnancy category	C
Nursing	It is not known whether this drug is excreted in human milk
Pediatric use	Safety and effectiveness have not been established in children <10 years of age

Supplemental Table VIII. Prescribing information for combination clindamycin and tretinoin

Indication	Topical treatment of acne vulgaris in patients ≥12 years of age
Dosing	Apply a pea-sized amount to the entire face once daily at bedtime.
Contraindications	Patients with regional enteritis, ulcerative colitis, or history of antibiotic–associated colitis.
Efficacy	In clinical trials, 21-41% of patients using combined clindamycin and tretinoin topically demonstrated successful treatment (using Evaluator's Global Severity score)
Adverse effects/toxicities	Erythema, scaling, itching, burning, stinging, nasopharyngitis, pharyngolaryngeal pain, dry skin, cough, and sinusitis
Interactions	Concomitant use of topical medications with a strong drying effect can increase skin irritation. Should not be used in combination with erythromycin-containing products. Should not be used in combination with neuromuscular blocking agents
Other issues	Avoid exposure to sunlight and sunlamps. Weather extremes, such as wind or cold, may be irritating
Pregnancy category	C
Nursing	It is not known whether clindamycin or tretinoin is excreted in human milk
Pediatric use	Safety and effectiveness have not been established in pediatric patients <12 years of age

Supplemental Table IX. Prescribing information for adapalene

Indication	Topical treatment of acne vulgaris in patients ≥12 years of age
Dosing	Apply a thin film of adapalene to the entire face and any other affected areas of the skin once daily in the evening, after washing gently with a nonmedicated soap
Contraindications	Should not be administered to individuals who are hypersensitive to adapalene or any of the components in the vehicle
Efficacy	Clinical studies show that 16% of patients applying 0.1% topical adapalene and 21% of patients applying 0.3% topical adapalene had successful treatments after 12 weeks (using Investigator's Global Assessment)
Adverse effects/toxicities	Erythema, scaling, dry skin, burning/stinging, skin discomfort, pruritus, desquamation, sunburn, allergic/hypersensitivity reactions, face/eyelid edema, lip swelling, and angioedema
Interactions	Has the potential to induce local irritation in some patients, concomitant use of other potentially irritating topical products should be approached with caution. Use with caution, especially when using preparations containing sulfur, resorcinol, or salicylic acid
Other issues	Exposure to sunlight, including sunlamps, should be minimized during use. Weather extremes, such as wind or cold, also may be irritating
Pregnancy category	C
Nursing	It is not known whether adapalene is excreted in human milk
Pediatric use	Safety and effectiveness have not been established in pediatric patients <12 years of age

Supplemental Table X. Prescribing information for combination adapalene and benzoyl peroxide

Indication	Topical treatment of acne vulgaris in patients ≥9 years of age
Dosing	Apply a thin film to affected areas of the face or trunk once daily after washing. Use a pea-sized amount for each area of the face (eg, forehead, chin, and each cheek)
Contraindications	Known hypersensitivity to adapalene or any ingredient in the formulation
Efficacy	In clinical trials, 21-47% of patients had successful treatment (using Investigator's Global Assessment)
Adverse effects/toxicities	Erythema, scaling, dryness, stinging/burning, contact dermatitis, skin irritation, eyelid edema, sunburn, blister, pain of skin, swelling face, conjunctivitis, skin discoloration, rash, eczema, throat tightness, and allergic contact dermatitis
Interactions	Keratolytic agents and photosensitizing agents
Other issues	Exposure to sunlight, including sunlamps, should be minimized. Weather extremes, such as wind or cold, may be irritating
Pregnancy category	C
Nursing	It is not known whether adapalene or benzoyl peroxide is excreted in human milk
Pediatric use	Safety and effectiveness in pediatric patients <9 years of age has not been established

Supplemental Table XI. Prescribing information for tazarotene

Indication	Topical treatment of acne vulgaris
Dosing	Apply a thin layer of tazarotene only to the affected area once daily in the evening
Contraindications	Pregnancy and hypersensitivity
Efficacy	Tazarotene was significantly more effective than vehicle in the treatment of facial acne vulgaris
Adverse effects/toxicities	Pruritus, burning, skin redness, peeling, desquamation, dry skin, and erythema
Interactions	Photosensitizing agents
Other issues	Avoid exposure to sunlight, sunlamps, and weather extremes
Pregnancy category	X
Nursing	It is not known whether this drug is excreted in human milk
Pediatric use	The safety and efficacy of tazarotene have not been established in patients with acne <12 years of age

Supplemental Table XII. Prescribing information for azelaic acid

Indication	Topical treatment of mild to moderate inflammatory acne vulgaris
Dosing	A thin film should be gently but thoroughly massaged into the affected areas twice daily, in the morning and evening
Contraindications	Known hypersensitivity to azelaic acid or any of its components
Adverse effects/toxicities	Pruritus, burning, stinging, tingling, erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis
Pregnancy category	B
Nursing	Minimally distributed into milk after topical application. Caution if used in nursing women
Pediatric use	Safety and effectiveness in pediatric patients <12 years of age have not been established

Supplemental Table XIII. Prescribing information for dapsone

Indication	Topical treatment of acne vulgaris
Dosing	Apply approximately a pea-sized amount, in a thin layer to the acne affected area, twice daily
Duration of dosing	If there is no improvement after 12 weeks, treatment should be reassessed
Contraindications	None
Efficacy	In clinical trials, 35-42% of patients using topical dapsone were successfully treated (using the Global Acne Assessment Score)
Adverse effects/toxicities	Oiliness, peeling, dryness, erythema, burning, pruritus, pyrexia, nasopharyngitis, upper respiratory infection, sinusitis, influenza, pharyngitis, cough, joint sprain, headache, suicide attempt, depression, psychosis, tonic clonic movements, abdominal pain, severe vomiting, and pancreatitis
Interactions	Trimethoprim/sulfamethoxazole, topical benzoyl peroxide, rifampin, anticonvulsants, St John's wort, and folic acid antagonists
Other issues	Some subjects with glucose 6 phosphate dehydrogenase deficiency developed changes suggestive of mild hemolysis. Observe for signs and symptoms of hemolysis, peripheral neuropathy, and skin reactions
Pregnancy category	C
Nursing	It is known that dapsone is excreted in human milk. Because of the potential for oral dapsone to cause adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue use
Pediatric use	Safety and efficacy was not studied in pediatric patients less than 12 years of age.

Supplemental Table XIV. Prescribing information for tetracycline

Indication	Adjunctive treatment in moderate to severe inflammatory acne
Dosing	Children >8 years of age: 25-50 mg/kg daily in 4 divided doses Adults: 1 g daily given in divided doses; when improvement occurs in 1-2 weeks, decrease slowly to a maintenance dosage of 125-500 mg daily
Duration of dosing	Adults: continue maintenance dosage until clinical improvement allows discontinuation of the drug.
Contraindications	Hypersensitivity to any of the tetracyclines
Adverse effects/toxicities	Gastrointestinal: anorexia, nausea, epigastric distress, vomiting, diarrhea, glossitis, black hairy tongue, dysphagia, enterocolitis, inflammatory lesions (with Candidal overgrowth) in the anogenital region, esophagitis, or esophageal ulceration Teeth: permanent discoloration during tooth development, enamel hypoplasia Skin: maculopapular and erythematous rashes, exfoliative dermatitis, onycholysis, nail discoloration, or photosensitivity Renal: rise in blood urea nitrogen (dose-related) Liver: hepatotoxicity and liver failure Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, and serum sickness–like reactions, as fever, rash, or arthralgia Blood: hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, neutropenia, or eosinophilia Other: bulging fontanels, intracranial pressure
Interactions	Antacids (eg, aluminum, calcium, magnesium containing), oral anticoagulants, atovaquone, didanosine, hormonal contraceptives, methoxyflurane, and penicillins
Other issues	Use as monotherapy should be avoided
Pregnancy category	D
Nursing	Distributed into milk; discontinue nursing or the drug
Pediatric use	Should not be used in children <8 years of age unless other appropriate drugs are ineffective or are contraindicated

Supplemental Table XV. Prescribing information for minocycline

Indication	Adjunctive treatment of moderate to severe inflammatory acne
Dosing	Children >8 years of age: 4 mg/kg initially followed by 2 mg/kg every 12 hours Adults: 50 mg 1-3 times daily
Contraindications	Hypersensitivity to minocycline, any tetracycline, or any component in the preparation
Adverse effects/toxicities	Body as a whole: fever and discoloration of secretions Gastrointestinal: anorexia, nausea, vomiting, diarrhea, dyspepsia, stomatitis, glossitis, dysphagia, enamel hypoplasia, enterocolitis, pseudomembranous colitis, pancreatitis, inflammatory lesions (with monilial overgrowth) in the oral and anogenital regions, esophagitis, and esophageal ulcerations Genitourinary: vulvovaginitis Hepatic toxicity: hyperbilirubinemia, hepatic cholestasis, increases in liver enzymes, fatal hepatic failure, and jaundice. Hepatitis, including autoimmune hepatitis, and liver failure Skin: alopecia, erythema nodosum, hyperpigmentation of nails, pruritus, toxic epidermal necrolysis, vasculitis, maculopapular and erythematous rashes, exfoliative dermatitis, fixed drug eruptions, lesions occurring on the glans penis have caused balanitis, erythema multiforme, Stevens—Johnson syndrome, photosensitivity, or pigmentation of the skin and mucous membranes Respiratory: cough, dyspnea, bronchospasm, exacerbation of asthma, or pneumonitis. Renal: interstitial nephritis, rise in blood urea nitrogen (dose-related), or reversible acute renal failure Musculoskeletal: arthralgia, arthritis, bone discoloration, myalgia, joint stiffness, and joint swelling. Hypersensitivity reactions: urticaria, angioneurotic edema, polyarthralgia, anaphylaxis/anaphylactoid reaction (including shock and fatalities), anaphylactoid purpura, myocarditis, pericarditis, exacerbation of systemic lupus erythematosus and pulmonary infiltrates with eosinophilia, transient lupus-like syndrome, and serum sickness—like reactions Blood: agranulocytosis, hemolytic anemia, thrombocytopenia, leukopenia, neutropenia, pancytopenia, and eosinophilia Central nervous system: convulsions, dizziness, hypesthesia, paresthesia, sedation, vertigo, bulging fontanels in infants and benign intracranial hypertension (pseudotumor cerebri) in adults, or headache Oral/teeth: tooth discoloration and oral cavity discoloration (including tongue, lip, and gum) Other: thyroid cancer, abnormal thyroid function, tinnitus, or decreased hearing
Interactions	Antacids (eg, aluminum, calcium, magnesium containing), oral anticoagulants, ergot alkaloids, hormonal contraceptives, iron-containing preparations, isotretinoin, methoxyflurane, and penicillins
Other issues	Use as monotherapy should be avoided
Pregnancy category	D
Nursing	Distributed into milk, discontinue nursing or the drug
Pediatric use	Should not be used in children <8 years of age unless benefits outweigh the risks

Supplemental Table XVI. Prescribing information for doxycycline

Indication	Adjunctive treatment in severe acne
Dosing	Children >8 years of age and <100 pounds: 2 mg/lb of body weight divided into 2 doses on the first day of treatment, followed by 1 mg/lb of body weight given as a single daily dose or divided into 2 doses, on subsequent days Adults and children >100 pounds: 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day
Contraindications	Hypersensitivity to any of the tetracyclines
Adverse effects/toxicities	Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, hepatotoxicity, esophagitis, or esophageal ulcerations Skin: toxic epidermal necrolysis, Stevens–Johnson syndrome, erythema multiforme, maculopapular and erythematous rashes, exfoliative dermatitis, or photosensitivity Renal: rise in blood urea nitrogen (dose-related) Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, or exacerbation of systemic lupus erythematosus Blood: hemolytic anemia, thrombocytopenia, neutropenia, or eosinophilia Other: bulging fontanels, intracranial pressure
Interactions	Antacids (eg, aluminum, calcium, magnesium containing), oral anticoagulants, anticonvulsants, bismuth subsalicylate, hormonal contraceptives, iron-containing preparations, methoxyflurane, penicillins, proton-pump inhibitors, oral retinoids, and urinary catecholamine assay
Other issues	Use as monotherapy should be avoided
Pregnancy category	D
Nursing	Distributed into milk. Discontinue nursing or the drug
Pediatric use	Safety and efficacy not established

Supplemental Table XVII. Prescribing information for trimethoprim sulfamethoxazole

Indication	Not approved by the US Food and Drug Administration for treatment of acne, use is off-label
Contraindications	Known hypersensitivity to trimethoprim or sulfonamides, history of drug-induced immune thrombocytopenia with use of trimethoprim or sulfonamides, patients with documented megaloblastic anemia caused by folate deficiency, pregnant patients and nursing mothers, pediatric patients <2 months of age, and patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored
Adverse effects/toxicities	Fatalities: Stevens–Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias Hematologic: agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia, thrombotic thrombocytopenia purpura, or idiopathic thrombocytopenic purpura Allergic reactions: Stevens–Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch–Schönlein purpura, serum sickness–like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticarial, rash, periarteritis nodosa, or systemic lupus erythematosus Gastrointestinal: hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, or anorexia Genitourinary: renal failure, interstitial nephritis, blood urea nitrogen and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria, and nephrotoxicity in association with cyclosporine Metabolic and nutritional: hyperkalemia Neurologic: aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, or headache Psychiatric: hallucinations, depression, apathy, or nervousness Endocrine: cross-sensitivity may exist with goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, diuresis, or hypoglycemia Musculoskeletal: arthralgia, myalgia, or rhabdomyolysis Respiratory: cough, shortness of breath, or pulmonary infiltrates Miscellaneous: weakness, fatigue, or insomnia
Interactions	Amantadine, tricyclic antidepressants, cyclosporine, digoxin, diuretics, oral hypoglycemic agents, indomethacin, methotrexate, phenytoin, pyrimethamine, tests for creatinine, and warfarin
Other issues	Use as monotherapy should be avoided
Pregnancy category	C, sulfonamides may cause kernicterus in neonates
Nursing	Both sulfamethoxazole and trimethoprim distributed into milk
Pediatric use	Safety and efficacy not established in children <2 months of age

Supplemental Table XVIII. Prescribing information for trimethoprim

Indication	Not approved by the US Food and Drug Administration for treatment of acne, use is off-label
Contraindications	Known hypersensitivity to trimethoprim, documented megaloblastic anemia caused by folate deficiency
Adverse effects/toxicities	Dermatologic: rash, pruritus, or phototoxic skin eruptions Hypersensitivity: exfoliative dermatitis, erythema multiforme, Stevens—Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome), or anaphylaxis Gastrointestinal: epigastric distress, nausea, vomiting, glossitis, elevation of serum transaminase and bilirubin, or cholestatic jaundice Hematologic: thrombocytopenia, leukopenia, neutropenia, megaloblastic anemia, or methemoglobinemia. Metabolic: hyperkalemia, hyponatremia Neurologic: aseptic meningitis Miscellaneous: fever, increases in blood urea nitrogen and serum creatinine levels
Interactions	Dapsone, phenytoin, tests for creatinine, test for methotrexate
Other issues	Use as monotherapy should be avoided
Pregnancy category	C, trimethoprim may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify risk to fetus
Nursing	Distributed into milk. Because trimethoprim may interfere with folic acid metabolism, use caution in nursing women
Pediatric use	Safety and efficacy not established, use with caution in children with fragile X chromosome because folate depletion way worsen psychomotor regression associated with the disorder

Supplemental Table XIX. Prescribing information for erythromycin (systemic)

Indication	Not approved by the US Food and Drug Administration for treatment of acne, use is off-label
Contraindications	Hypersensitivity to erythromycins, patients taking terfenadine, astemizole, pimozide, or cisapride
Adverse effects/toxicities	Gastrointestinal: pseudomembranous colitis, nausea, vomiting, abdominal pain, diarrhea, or anorexia Liver: hepatitis, hepatic dysfunction, or abnormal liver function results Cardiovascular: QT prolongation, ventricular tachycardia, or torsades de pointes Allergic reaction: urticaria to anaphylaxis Skin reaction: mild eruptions to erythema multiforme, Stevens–Johnson syndrome, or toxic epidermal necrolysis Other: pancreatitis, convulsion, or reversible hearing loss
Interactions	Antiarrhythmic agents, oral anticoagulants, azole antifungals, benzodiazepines, calcium-channel blocking agents, carbamazepine, chloramphenicol, cisapride, clindamycin/lincomycin, ergot alkaloids, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, cyclosporine, pimozide, sildenafil, and theophylline
Other issues	Use as monotherapy should be avoided
Pregnancy category	B
Nursing	Distributed into milk, use with caution
Pediatric use	Safety and efficacy not established

Supplemental Table XX. Prescribing information for azithromycin

Indication	Not approved by the US Food and Drug Administration for the treatment of acne, use is off-label
Contraindications	Hypersensitivity to azithromycin, erythromycin, any macrolide, or any ketolide; history of cholestatic jaundice/hepatic dysfunction associated with previous use of azithromycin
Adverse effects/toxicities	Cardiovascular: palpitations, chest pain, arrhythmias, QT prolongation, or torsade de pointes Gastrointestinal: dyspepsia, flatulence, diarrhea, loose stools, nausea, vomiting, abdominal pain, melena, cholestatic jaundice, anorexia, constipation, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, or tongue discoloration Genitourinary: monilial, vaginitis, nephritis, or acute renal failure Nervous system: dizziness, headache, vertigo, somnolence, convulsions, hyperactivity, nervousness, agitation, or syncope Liver/biliary: hepatic dysfunction Skin/appendages: pruritus, erythema multiforme, Stevens—Johnson syndrome, or toxic epidermal necrolysis General: fatigue, asthenia, paresthesia, malaise, anaphylaxis, hearing loss, deafness, tinnitus, or taste/smell perversion/loss Allergic: rash, pruritus, photosensitivity, angioedema, arthralgia, edema, or urticarial Hematopoietic: thrombocytopenia
Interactions	Albendazole, antacids (eg, aluminum, magnesium containing), anticoagulants, antimycobacterials (eg, rifamycins), atazanavir, benzodiazepines, carbamazepine, cetirizine, chloroquine, cimetidine, cotrimoxazole, cyclosporine, didaosine, digoxin, efavirenz, ergot alkaloids, hexobarbital, 3-hydroxy-3-methylglutaryl-coenzyme A inhibitors, indinavir, ivermectin, lopinavir, nelfinavir, phenytoin, pimozide, quinine, sildenafil, theophylline, and zidovudine
Other issues	Use as monotherapy should be avoided
Pregnancy category	B
Nursing	Distributed into milk, use with caution
Pediatric use	Safety and efficacy not established

Supplemental Table XXI. Prescribing information for amoxicillin

Indication	Adjunctive treatment in acne, especially during pregnancy
Dosing	Children: mild to moderate skin infections: >3 months and <40 kg, 25 mg/kg/day orally every 2 hours OR 20 mg/kg/day every 8 hours; >3 months and >40 kg 500 mg orally every 12 hours or 250 mg orally every 8 hours Adults: 250 mg twice a day up to 500 mg 3 times a day
Contraindications	Known hypersensitivity to penicillins, including serious hypersensitivity reactions, such as anaphylaxis and Stevens–Johnson syndrome to penicillins and cephalosporins
Adverse effects/toxicities	Skin: acute generalized exanthematous pustulosis, erythematous maculopapular rash, urticaria, erythema multiforme, Stevens–Johnson syndrome, or toxic epidermal necrolysis Gastrointestinal: diarrhea, nausea, or vomiting Neurologic: headache, agitation, anxiety, behavior changes, dizziness, insomnia, or seizure Immunologic: anaphylaxis, hypersensitivity reaction, or serum sickness Blood: agranulocytosis, anemia, eosinophilia, hemolytic anemia, leucopenia, thrombocytopenia, or thrombocytopenia purpura Hepatic: cholestatic hepatitis, cholestatic jaundice, hepatitis, or increased aspartate transaminase and alanine transaminase
Interactions	Venlafaxine, methotrexate, tetracyclines, warfarin, bupropion and other agents lowering seizure threshold, probenecid, acenocoumarol, khat, phenindione, piperine, dicumarol, phenprocoumon, and allopurinol
Other issues	Renal dosing adjustment required
Baseline monitoring	None
Pregnancy category	B
Nursing	Minimal risk to infant, compatible with breastfeeding
Pediatric use	Safety and efficacy established

Supplemental Table XXII. Prescribing information for cephalexin

Indication	Adjunctive treatment in acne
Dosing	Children: 25-50 mg/kg/day every 6-8 hours Adults: 500 mg twice a day
Contraindications	Hypersensitivity to cephalosporins
Adverse effects/toxicities	Central nervous system: agitation, confusion, dizziness, fatigue, or headache Skin: erythema multiforme, genital pruritus, Stevens—Johnson syndrome, toxic epidermal necrolysis, or urticaria Gastrointestinal: abdominal pain, diarrhea, dyspepsia, gastritis, nausea, pseudomembranous colitis, or vomiting Genitourinary: genital candidiasis, vaginal discharge, or vaginitis Blood: eosinophilia, hemolytic anemia, neutropenia, or thrombocytopenia Hepatic: cholesatatic jaundice, hepatitis, or increased aspartate transaminase and alanine transaminase Immunologic: anaphylaxis, angioedema, or hypersensitivity reaction Skeletal: arthralgia, arthritis Renal: interstitial nephritis
Interactions	Warfarin, metformin, multivitamins with folate, iron, cholestyramine, live typhoid vaccine, and zinc salts
Other issues	Renal impairment requires dose adjustments
Baseline monitoring	None
Pregnancy category	B
Nursing	Infant risk is minimal
Pediatric use	Safety and efficacy established

Supplemental Table XXIII. Prescribing information for ethinyl estradiol/norgestimate

Indication	Acne vulgaris
Dosing	1 tablet orally daily at the same time Children: after menarche, 1 tablet daily at the same time
Contraindications	Blood pressure: systolic >160 mm Hg, diastolic >100 mm Hg, or severe hypertension Carcinoma of the breast Carcinoma of the endometrium Cerebral vascular or coronary artery disease Cholestatic jaundice of pregnancy or jaundice with previous pill use Deep vein thrombosis or thromboembolic disorders Diabetes with vascular involvement Genital bleeding, undiagnosed Headaches with focal neurologic symptoms Hepatic adenomas or carcinomas Hepatocellular disease with abnormal liver function Hypersensitivity Valvular heart disease with complications Surgery with prolonged immobilization
Adverse effects/Toxicities	Cardiovascular: edema, varicose veins aggravation Central nervous system: depression, migraine, or mood changes Skin: cholasma, melasma, or erythema nodosum Endocrine: amenorrhea, breakthrough bleeding, breast pain/tenderness, fluid retention, or infertility Gastrointestinal: abdominal bleeding, abdominal cramps, appetite changes, nausea, weight changes, or vomiting Genitourinary: cervical ectropion, cervical secretion, vaginal candidiasis, or vaginitis Blood: folate decreased, porphyria exacerbation Hepatic: cholestatic jaundice Anaphylaxis, lupus exacerbation
Interactions	Many antibiotics (cephalosporins, chloarmphenicol, macrolides, penicillins, tetracyclines, or sulfas), aprepitant, bexarotene, bosentan, dapsonse, griseofluvin, HIV protease inhibitors (amprenavir, nelfinavir, and ritonavir), modafinil, nevirapine, rifampin, seizure medications (barbiturates, carbamazepine, phenytoin, primidone, and topiramate), St John's wort, tranexamic acid, clozapine, carbamazpine, tizanidine, felbamate, dabrafenib, pirfenidone, apiprazole, paclitaxel, fentanyl, theophylline, eligustat, siltuximab, isotretinoin, mitotane, crizotinib, bupropion, certinib, piperaquine, troleadndomycin, fosamprenavir, voriconazole, rifampin, prednisolone, tipanavir, telaprevir, lamotrigine, rifbutin, rosuvastatin, nelfinavir, phenytoin, licorice, alprazolam, modafinil, bexarotene, topiramate, warfarinbosentan, amprenavir, seleginline, ginseng, mycophenolate mofetil, and piglitazone
Baseline monitoring	Pregnancy status, blood pressure
Ongoing monitoring	Assess potential health status
Pregnancy category	X
Nursing	Both ethinyl estradiol and norgestimate are compatible with breastfeeding
Pediatric use	Use before menarche is not indicated

Supplemental Table XIV. Prescribing information for ethinyl estradiol/norethindrone acetate/ferrous fumarate

Indication	Adjuvant therapy for acne
Dosing	Teens ≥15 years of age and adults: 1 pill a day every day at the same time for 21 days followed by 1 week of no tablets
Contraindications	Anaphylactic reaction or angioedema Active or history of arterial thromboembolic disease (stroke or myocardial infarction) Breast cancer Carcinoma of the endometrium Cerebral vascular or coronary artery disease Cholestatic jaundice of pregnancy or jaundice with previous pill use Deep vein thrombosis or thromboembolic disease, pulmonary embolism Undiagnosed genital bleeding Hepatic adenomas or carcinomas Hepatic disease Pregnancy
Adverse effects/toxicities	Central nervous system: headache, depression, or nervousness Mood disorder Endocrine: breast pain, irregular menstruation, menorrhagia, or weight changes Gastrointestinal: abdominal pain, nausea, vomiting, diarrhea, or dyspepsia Genitourinary: urinary tract infections, vaginitis, or abnormal uterine bleeding Infection: viral infection Respiratory: sinusitis
Interactions	Acitretin, anticoagulants, aprepitant, aripiprazole, barbiturates, bexrotene, boceprevir, bosentan, anticonvulsants, dabrafenib, mifepristone, modafinil, mycophenolate, antibiotics, nonsteroidal antiinflammatory drugs, protease inhibitors, St John's wort, telaprevir, thalidomide, topiramate, vitamin K antagonist, or voriconazole
Baseline monitoring	Assessment of pregnancy status, blood pressure
Ongoing monitoring	Blood pressure, monitor health status changes
Pregnancy category	X
Nursing	World Health Organization: avoid breastfeeding if possible, infant risk cannot be ruled out
Pediatric use	Safety and efficacy not established

Supplemental Table XXV. Prescribing information for ethinyl estradiol/drospirenone

Indication	Acne vulgaris, hormonal therapy
Dosing	Women: 1 tablet daily at the same time every day
Contraindications	Renal dysfunction, adrenal insufficiency
	Breast cancer or other estrogen- or progestin-sensitive cancer
	Cerebrovascular disease, coronary artery disease
	Current or history of deep vein thrombosis or pulmonary embolism
	Headaches with focal neurologic symptoms or migraine headaches with or without aura >35 years of age
	Hepatic dysfunction, hepatic tumors benign or malignant
	Hypercoagulopathies
	Hypertension, uncontrolled
	Pregnancy
	Smoking if >35 years of age
	Undiagnosed uterine bleeding
	Thrombogenic valvular or thrombogenic rhythm diseases
Adverse effects/toxicities	Cardiovascular: edema, varicose vein aggravation, increase risk of arterial thromboembolism, cerebral thrombosis, hypertension, or myocardial infarction
	Gastrointestinal: abdominal bloating, abdominal cramps, nausea, weight changes, or vomiting
	Central nervous system: depression, migraine
	Skin: melasma, allergic rash
	Endocrine: amenorrhea, breakthrough bleeding, breast changes, infertility, carbohydrate tolerance decreased, or spotting
	Genitourinary: cervical ectropion, cervical secretion, or vaginal candidiasis
	Blood: folate decreased, porphyria exacerbation
	Hepatic: cholestatic jaundice
	Ocular: contact lens intolerance, corneal curvature changes
	Other: anaphylactic, systemic lupus erythematosus exacerbation
Interactions	Drospirenone, tranexamic acid, anticonvulsants, antibiotics (cephalosporins, macrolides, penicillins, tetracyclines, and sulfas), aprepitant, bexarotene, bosentan, griseofulvin, HIV protease inhibitors, modafinil, nevirapine, St John's wort, acitretin, opioids, angiotensin II receptor blockers, anticoagulants, aprepitant, barbiturates, monoamine oxidase inhibitors, mifepristone, thalidomide, and voriconazole
Baseline monitoring	Breast and pelvic examinations, including Papanicolaou smear, urine pregnancy test, and blood pressure
Ongoing monitoring	Blood pressure, assess potential health status changes
Pregnancy category	X
Nursing	World Health Organization: avoid breastfeeding
	American Academy of Pediatrics: maternal medication usually compatible with breastfeeding
Pediatric use	Safety and efficacy established if started after menarche

Supplemental Table XXVI. Prescribing information for ethinyl estradiol/drospirenone/levomefolate

Indication	Acne vulgaris, hormonal therapy
Dosing	Women after the beginning of menses: 1 pink tablet orally every day for 24 consecutive days followed by 1 orange table daily for 4 days
	Begin therapy either on the first day of menstrual period on the first Sunday after the onset of menstruation
	May be initiated 4 weeks postpartum in nonlactating mothers
Contraindications	Adrenal insufficiency
	Breast cancer or other estrogen- or progestin-sensitive cancer
	Cerebrovascular disease
	Coronary artery disease
	Current or history of deep vein thrombosis or pulmonary embolism
	Diabetes with vascular disease
	Headaches with focal neurologic symptoms or migraine headaches with or without aura if >35 years of age
	Hepatic tumors, benign or malignant
	Hepatic disease
	Hypercoagulopathies, inherited or acquired
	Uncontrolled hypertension
	Pregnancy
	Renal impairment
	Smoking and ≥35 years of age
	Thrombogenic valvular or thrombogenic rhythm disease of the heart
	Undiagnosed uterine bleeding
Adverse effects/toxicities	Endocrine: weight increase, hyperkalemia, or impaired glucose tolerance
	Cardiovascular: arterial thromboembolism, deep vein thrombosis, hypertension, or myocardial infarction
	Gastrointestinal: abdominal pain, nausea, vomiting, gallbladder disorder, or pancreatitis
	Hepatic: cholasma, cholestasis, or neoplasm of liver
	Neurologic: headache, hemorrhagic cerebral infarction, migraine, or thrombotic stroke
	Blood: thromboembolic disorder, porphyria exacerbation
	Psychiatric: depression, irritability, or labile effect
	Reproductive: break through bleeding, breast tenderness, disorder of menstruation, reduced libido, or dysplasia of the cervix
	Immunologic: anaphylaxis
	Eyes: thrombosis of retinal vein
	Respiratory: pulmonary embolism
Interactions	Drospirenone, tranexamic acid, anticonvulsants, antibiotics (cephalosporins, macrolides, penicillins, tetracyclines, and sulfas), aprepitant, bexarotene, bosentan, griseofulvin, HIV protease inhibitors, modafinil, nevirapine, St John's wort, acitretin, opioids, angiotensin II receptor blockers, anticoagulants, aprepitant, barbiturates, monoamine oxidase inhibitors, mifepristone, potassium sparing diuretics, thalidomide, and voriconazole
Baseline monitoring	Breast and pelvic examinations, including Papanicolaou smear, urine pregnancy test, and blood pressure
Ongoing monitoring	Overall general health watching for thromboembolic symptoms, signs of depression, glycemic control in those with diabetes, and serum potassium in those taking medications with potassium-retaining properties
Pregnancy category	X
Nursing	Infant risk cannot be ruled out
Pediatric use	Safety and efficacy established if started after menarche

Supplemental Table XXVII. Prescribing information for spironolactone

Indication	Off-label use for acne vulgaris in females
Dosing	Adult: 50-200 mg orally daily
Duration of dosing	10 months
Contraindications	Acute renal failure, Addison disease, hyperkalemia, anuria, concomitant eplerenone or triamterene use, and significant renal impairment
Adverse effects/toxicities	Endocrine: gynecomastia, electrolyte disturbances, hyperkalemia, metabolic acidosis, or potential feminization male fetus if taken during pregnancy Gastrointestinal: diarrhea, nausea, vomiting, gastric hemorrhage, or gastritis Skin: erythematous maculopapular rash, Stevens–Johnson syndrome, or toxic epidermal necrolysis Neurologic: somnolence, confusion, or headache Blood: agranulocytosis Immunologic: drug hypersensitivity syndrome, systemic lupus erythematosus Reproductive: amenorrhea, irregular menses, postmenopausal bleeding, or erectile dysfunction Renal: increased blood urea nitrogen, renal failure, or renal insufficiency Other: breast cancer
Interactions	Triamterene, eplerenone, sulfamethoxazole/trimethoprim, angiotensin-converting enzyme inhibitors, digoxin, sotalol, droperidol, tacrolimus, amiloride, nitrofurantoin, pentoxifyline, phosphodiesterase 5 inhibitors, quinidine, rituzimab, tolvaptan, lithium, arsenic trioxide, potassium, angiotensin II receptor blockers, nonsteroidal antiinflammatory agents, digitoxin, licorice, morphine, yohimbine, and oxycodone
Ongoing monitoring	Serum potassium, sodium, and renal function
Pregnancy category	C
Nursing	Compatible with breastfeeding infant risk is minimal
Pediatric use	Safety or efficacy not established

Supplemental Table XXVIII. Prescribing information for flutamide

Indication	Acne, antiandrogen effect
Dosing	250-500 mg orally daily
Contraindications	Hypersensitivity to flutamide Severe hepatic impairment
Adverse effects/toxicities	Skin: rash, ecchymosis, or pruritus Endocrine: hot sweats, galactorrhea, or decreased libido Gastrointestinal: diarrhea, nausea, anorexia, constipation, or dyspepsia Genitourinary: impotence, cystitis, or breast tenderness Blood: anemia, leukopenia, or thrombocytopenia Hepatic: hepatoxicity, liver failure Central nervous system: anxiety, confusion, depression, dizziness, headache, or insomnia
Baseline monitoring	Liver function tests
Interactions	Warfarin, teriflunomide, corfelemer, dabrafenib, elvitegr-cobicist-emtric-tenof, iloperidone, crofelemer, and iloperidone
Ongoing monitoring	Liver function tests monthly for 4 months, then periodically especially if noted symptoms of liver dysfunction
Pregnancy category	D (should not be used in females)
Nursing	Infant risk cannot be ruled out
Pediatric use	Safety and effectiveness not established in children

Supplemental Table XXIX. Prescribing information for isotretinoin

Indication	Recalcitrant nodulocystic acne
Dosing	Severe: ≥12 years of age: 0.5-1 mg/kg/day orally in 2 divided doses with food Moderate: ≥12 years of age: 0.3-0.5 mg/kg/day Adults: 0.5-1 mg/kg/day
Duration of dosing	15-20 weeks
Contraindications	Hypersensitivity to isotretinoin or any of its components Hypersensitivity to vitamin A Pregnancy
Adverse effects/Toxicities	Cardiovascular: chest pain, edema, flushing, palpitation, stroke, syncope, or thrombosis Central nervous system: aggressive behavior, depression, emotional instability, fatigue, headache psychosis, suicidal ideation/attempts, violent behavior, stroke, pseudotumor cerebri, or seizure Skin: alopecia, cheilitis, cutaneous allergic reaction, dry nose, dry skin, eruptive xanthomas, nail dystrophy, photosensitivity Endocrine: abnormal menses, elevated glucose, cholesterol increased, hyperuricemia, or elevated triglycerides Gastrointestinal: bleeding and inflammation of gums, colitis, esophagitis, inflammatory bowel disease, nausea, or pancreatitis Blood: agranulocytosis, anemia, neutropenia, pyogenic granuloma, or thrombocytopenia Hepatic: increased aspartate transaminase and alanine transaminase/alkaline phosphatase, hepatitis, elevated lactate dehydrogenase Musculoskeletal: arthralgia, arthritis, back pain, hypertrophy of bone, increased creatinine kinase, or rhabdomyolysis Ocular: dry eyes, optic neuritis Otic: hearing loss Respiratory: bronchospasms, epistaxis
Interactions	Tetracyclines, vitamin A, methotrexate, contraceptives, or alcohol
Baseline monitoring	Liver function test, pregnancy test, or lipid panel
Ongoing monitoring	Pregnancy test every 30 days for females Repeat liver function tests and lipid panel at least once during treatment
Pregnancy category	X
Nursing	Not yet determined
Pediatric use	Safety and effectiveness not established in children <12 years of age

Supplemental Table XXX. Prescribing information for intralesional corticosteroid (triamcinolone acetonide)

Indication	Inflammatory nodulocystic acne and acne keloidalis
Dosing	Nodular acne: triamcinolone acetonide in 10 mg/mL. May be diluted with sterile normal saline to 5 or 3.3 mg/mL
	Acne keloidalis: triamcinolone acetonide -10 into inflammatory follicular lesions
	Triamcinolone acetonide -40 into hypertrophic scars and keloids
Contraindications	Should not be injected at the site of active infections, such as impetigo or herpes
	Should not be used if previous hypersensitivity to triamcinolone
	Large injections should be avoided in those with active tuberculosis or systemic fungal infection
	Extensive plaque psoriasis, pustular psoriasis, or erythrodermic psoriasis
	Active peptic ulcer disease
	Uncontrolled diabetes, heart failure, or severe hypertension
	Severe depression or psychosis
Short-term results/response	Flatten most acne nodules in 48 to 72 hours
Efficacy	Efficacious for an occasional or particularly stubborn cystic lesion
	Not an effective treatment strategy for patients with multiple lesions
Adverse effects/toxicities	Local overdose can result in atrophy, pigmentary changes, and telangiectasias, hypertrichosis
	Infections
	Impaired wound healing
	Contact allergic dermatitis caused by the preservative, benzyl alcohol
	Sterile abscess
	Steroid acne
	Repeated injections can suppress the hypothalamic-pituitary-adrenal axis
	Anaphylaxis, angioedema, and urticaria

Supplemental Table XXXI. Prescribing information for glycolic acid peels

Indication	Acne vulgaris and acne scars
Dosing	Available as free acids, partially neutralized (higher pH), buffered, or esterified solutions Available concentrations range from 20-70% Very superficial: 30-50% glycolic acid applied for 1-2 min Superficial: 50-70% applied for 2-5 min Medium depth: 70% applied for 3-15 min
Duration of dosing	Once every 15 days for 4-6 months
Contraindications	Lack of psychological stability and mental preparedness Unrealistic expectations Poor general health and nutritional status Isotretinoin therapy within the last 6 mos Active infection or open wounds (eg, herpes simplex, excoriations, or open acne cysts) Relative contraindications History of abnormal scar formation or delayed wound healing History of therapeutic radiation exposure History of rosacea, seborrheic dermatitis, atopic dermatitis, psoriasis, vitiligo, or active retinoid dermatitis For medium and deep peels: medium-depth or deep resurfacing procedure within the last 3-12 months For medium and deep peels: recent facial surgery involving extensive undermining
Adverse effects/toxicities	Postinflammatory hyperpigmentation Erosive blisters and scarring

Supplemental Table XXXII. Prescribing information for salicylic acid peels

Indication	Comedonal acne
Dosing	Concentrations of 20-30% are available Very superficial: 20% salicylic acid Superficial: 30% salicylic acid Applied for 2-4 minutes depending on intensity of clinical response
Contraindications	Lack of psychological stability and mental preparedness Unrealistic expectations Poor general health and nutritional status Isotretinoin therapy within the last 6 months Active infection or open wounds (eg, herpes simplex, excoriations, or open acne cysts) Relative contraindications History of abnormal scar formation or delayed wound healing History of therapeutic radiation exposure History of rosacea, seborrheic dermatitis, atopic dermatitis, psoriasis, vitiligo, or active retinoid dermatitis For medium and deep peels: medium-depth or deep resurfacing procedure within the last 3-12 months For medium and deep peels: recent facial surgery involving extensive undermining
Adverse effects/toxicities	Mild stinging and discomfort, burning, erythema, and mild to intense exfoliation

Supplemental Table XXXIII. Prescribing information for combination resorcinol and salicylic acid

Indication	Acne
Dosing	Cream, cloth, foam, or liquid cleansers 2%: use to clean face once or twice a day Gel 0.5% or 2%: apply small amount to face twice a day Pads 0.5% or 2%: use pad to cover affected area 1-3 times a day Patch 2%: use at bedtime, after washing face and allowing face to dry at least 5 min. Apply patch directly over pimple being treated. Remove in the morning
Contraindications	Hypersensitivity to salicylic acid
Adverse effects/toxicities	Central nervous system: dizziness, headache, and mental confusion Local: burning and irritation, peeling, and scaling Otic: tinnitus Respiratory: hyperventilation