Article Type: From the Academy

Title: Guidelines of care for the management of acne vulgaris

Rachel V. Reynolds, MD (Co-Chair)[a], Howa Yeung, MD MSc[b], Carol E. Cheng, MD[c], Fran Cook-Bolden, MD[d], Seemal R. Desai, MD[e], Kelly Druby[f], Esther E. Freeman, MD, PhD [g], Jonette E. Keri, MD, PhD[h,i], Linda F. Stein Gold, MD[j], Jerry K. L. Tan[k], Megha M. Tollefson, MD[l], Jonathan S. Weiss, MD[m], Peggy A Wu, MD, MPH[n], Andrea L. Zaenglein, MD[o], Jung Min Han, PharmD, MS[p], John S. Barbieri, MD, MBA (Co-Chair)[q]

Department of Dermatology, Beth Israel Deaconess Medical Center, Boston, Massachusetts[a]; Department of Dermatology, Emory University School of Medicine, Atlanta, Georgia[b]; Division of Dermatology, Department of Medicine, University of California Los Angeles, Los Angeles, California [c]; Mount Sinai Beth Israel, New York, New York[d]; Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, Texas[e]; Penn State Health Hampden Medical Center, Enola, PA[f]; Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts[g]; Miami VA Medical Center, Miami, Florida [h]; University of Miami, Miller School of Medicine [i], Department of Dermatology, Henry Ford Health, Detroit, Michigan[j]; Windsor Clinical Research Inc.[k]; Departments of Dermatology and Pediatrics, Mayo Clinic, Rochester, Minnesota[l]; Georgia Dermatology Partners, Snellville, GA[m]; Department of Dermatology, University of California Davis, Sacramento, California[n]; Departments of Dermatology and Pediatrics, Penn State/ Hershey Medical Center, Hershey, Pennsylvania[o]; American Academy of Dermatology, Rosemont, Illinois[p]; Department of Dermatology, Brigham and Women's Hospital, Boston, Massachusetts[q]

Corresponding author:
Jung Min Han, PharmD, MS
American Academy of Dermatology
9500 Bryn Mawr Avenue, Suite 500
Rosemont, IL 60018
Email: jminhan@aad.org

Funding sources: This study was funded in total by internal funds from the American Academy of Dermatology.

Conflicts of Interest: Listed in text.

Supplementary files are available on: Mendeley Link pending

Reprint Requests: Jung Min Han

Manuscript word count: words [excluding abstract, references, figures, tables, appendix]
Abstract word count:
References:
Figures: 1
Tables: 4
Online Supplementary figures: 179
Online Supplementary tables: 177

Keywords: Acne, acne vulgaris, treatment, guidelines, retinoids, adapalene, tretinoin, tazarotene, trifarotene, benzoyl peroxide, salicylic acid, azelaic acid, clindamycin, erythromycin, doxycycline, minocycline, sarecycline, azithromycin, antibiotics, clascoterone, contraceptives, spironolactone,

hormonal therapy, antiandrogens, isotretinoin, light therapies, corticosteroids, grading and classification of acne, diet and acne, microbiological and endocrine testing, *Cutibacterium acnes*

PUBLISHABLE CONFLICT OF INTEREST STATEMENT

The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies' Code of Interactions with Companies. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at www.aad.org.

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 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.

ABSTRACT

Background: Acne vulgaris commonly affects adults, adolescents, and preadolescents aged 9 years or above.

Objective: To provide evidence-based recommendations for the management of acne

Methods: A Work Group conducted a systematic review and applied the Grading of Recommendations, Assessment, Development, and Evaluation approach for assessing the certainty of evidence and formulating and grading recommendations.

Results: This guideline presents 18 evidence-based recommendations and 5 good practice statements. Strong recommendations are made for benzoyl peroxide, topical retinoids, topical antibiotics, and oral doxycycline. Oral isotretinoin is strongly recommended for acne that is severe, causing psychosocial burden or scarring, or failing standard oral or topical therapy. Conditional recommendations are made for topical clascoterone, salicylic acid, and azelaic acid, as well as for oral minocycline, sarecycline, combined oral contraceptive pills, and spironolactone. Combining topical therapies with multiple mechanisms of action, limiting systemic antibiotic use, combining systemic antibiotics with topical therapies, and adding intralesional corticosteroid injections for larger acne lesions are recommended as good practice statements.

Limitations: Analysis is based on the best available evidence at the time of the systematic review.

Conclusions: These guidelines provide evidence-based recommendations for the management of acne vulgaris.

ABBREVIATIONS

BP: benzoyl peroxide

COC: combined oral contraceptives

EE: ethinyl estradiol

FDA: Food and Drug Administration

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation

IBD: inflammatory bowel disease

IGA: Investigator Global Assessment

MD: mean difference

RCT: randomized controlled trials

RR: risk ratio

US: United States

SCOPE & OBJECTIVES

Acne vulgaris is one of the most common skin conditions diagnosed and treated by dermatologists in the United States (US) and worldwide.[1, 2] These guidelines aim to provide evidence-based recommendations to guide the clinical management of acne vulgaris for adults, adolescents, and preadolescents aged 9 years or above from the perspectives of US and Canadian dermatologists, clinicians who treat acne, and patients. These guidelines update the 2016 American Academy of Dermatology guidelines of care for the management of acne.[3] We examine evidence based on a systematic review of the literature on acne grading and classification, laboratory testing, and treatment using topical therapies, systemic antibiotics, hormonal agents, oral isotretinoin, physical modalities, complementary and alternative medicine, and dietary and environmental interventions. These guidelines focus on acne treatments that are available, approved by the US Food and Drug Administration (FDA), and commonly used in the US. Acneiform eruptions and medication-induced acne are not addressed. Diagnosis and treatment of infantile acne, mid-childhood acne in children under the age of 9, and acne-induced hyperpigmentation and scarring are beyond of the scope of these guidelines.[4]

METHODS

AAD and Evidinno, Inc. conducted a series of focused and systematic reviews from May 2021 to November 2022 (see **Detailed Methods** in **Supplemental Materials**) to determine the effectiveness and safety of treatments currently available and approved in the US for the management of acne vulgaris in adults, adolescents, and preadolescents aged 9 years or above based on the nine clinical questions with pre-specified patient, intervention, comparator, and outcome (PICO) and study eligibility criteria (**Table I** and **e-Tables 1-7**). The Work Group consisted of 9 board-certified dermatologists (including 1 methodologist and 1 measure representative and medical writer), 3 board-certified pediatric dermatologists, 1 staff liaison, and 1 patient representative. The Work Group employed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach for assessing the

certainty of the evidence and formulating and grading clinical recommendations. This approach incorporates benefits and harms, patient values and preferences, resource use, and certainty of evidence as key factors in the evidence to decision framework (e-Table 10). Strength of recommendation and strength of the supporting evidence were expressed as shown in **Table II**. [5-7] A strong recommendation means that the Work Group believes that the benefits clearly outweigh risks and burden (or that the risks and burden clearly outweigh the benefits), and a conditional recommendation means that the WG believes that the benefits are finely balanced with risks and burden. A conditional recommendation implies that we believe most people would want the recommended course of action.

DEFINITION

Acne vulgaris is a chronic, inflammatory skin disease of the pilosebaceous unit.[8] Acne primarily presents with open or closed comedones, papules, pustules, or nodules on the face or trunk and may result in pain, erythema, hyperpigmentation, or scars.[8]

INTRODUCTION/BACKGROUND

Acne vulgaris is a common skin condition affecting 9.4% of the global population in 2010, representing the eighth most prevalent disease globally.[9] Acne affects approximately 85% of teenagers but can occur in most age groups and can persist into adulthood.[10] The burden of acne, as measured by disability-adjusted life years, ranked second among all skin diseases in 2013.[11] Over 50 million people in the US have acne.[12] In the US, more than 5.1 million Americans sought medical treatment for acne, leading to $846 million in medical costs and $398 million in lost productivity for patients and caregivers in 2013.[1] Acne has important impact on emotional functioning, social functioning, relationships, leisure activities, daily activities, sleep, school, and work.[13, 14] The health-related quality of life impact of acne is comparable to that of chronic conditions such as asthma, psoriasis, and arthritis.[15, 16] Acne is associated with increased risks of stigmatization, bullying, depression, anxiety, poor self-esteem, and suicidal ideation.[17-20]

Multifactorial pathogenesis of acne involves follicular hyperkeratinization, microbial colonization with *Cutibacterium acnes*, sebum production, complex inflammatory mechanisms involving both innate and acquired immunity, neuroendocrine mechanisms, genetic and non-genetic factors. Risk factors for acne development include increasing age during adolescence, family history of acne, and oily skin type.[21]

ACNE GRADING AND CLASSIFICATION

Numerous acne clinical grading and classification systems have been used in research and clinical settings to assess overall acne disease severity, lesion number and morphologies, affected anatomical sites, and associated secondary changes such as dyspigmentation and scarring. Consistent use of an acne grading and classification system may help facilitate therapeutic decision-making and assess treatment response in clinical practice.[22] Available grading systems include the Investigator Global Assessment (IGA), Leeds revised acne grading system, Global Acne Grading System, Global Acne Severity (GEA) Scale, and Comprehensive Acne Severity Scale, among others.[23-29]

While there is no universally accepted acne grading system in clinical settings, the IGA is most commonly used in the US[30] and demonstrates good agreement between clinician and patient ratings. The definition of IGA scales varied over time and will require harmonization efforts to facilitate use and future meta-analyses.[31] The IGA scale has been used in many randomized controlled trials (RCT) for acne treatments and proposed as a cohesive framework upon which to establish an ideal acne grading system.[32] An ideal acne grading system should measure the types of primary acne lesions, number of lesions, extent and region of skin involvement and should feature strong psychometric properties, ability to categorize severity via descriptive text or photographs, ease of use, and stakeholder acecptance.[33] Stakeholders from the International Dermatology Outcomes Measures and the American Academy of Dermatology reached consensus on a 5-point ordinal scale (ranging from 0-4: clear, almost clear, mild, moderate, and severe) to quantify severity of acne and other inflammatory dermatoses in routine clinical practice.[34] Descriptors of this scale remain to be standardized and validated for use in facial and truncal acne. Acne severity may also be measured via digital photography, as is increasingly used in clinical practice and trials, as well as

fluorescent photography, polarized light photography, video microscopy, and multi-spectral imaging modalities.[35]

Beyond signs and symptoms, core acne outcomes measures should also include domains such as satisfaction with appearance, extent of scars/dark marks, satisfaction with treatment received, long-term acne control, adverse events, and health-related quality of life. Acne quality of life measures provide a more comprehensive and holistic perspective on the burden of acne on patients' lives and may not correlate well with clinical acne severity.[36] While multiple dermatology-specific and acne-specific health-related quality of life measures are available as research tools, shorter measures also exist for use in routine clinical practice.[37, 38]

MICROBIOLOGICAL AND ENDOCRINE TESTING

Cutibacterium acnes (formerly *Propionibacterium acnes)* is a Gram-positive anaerobic rod primarily implicated in acne pathogenesis, with some strains likely pathogenic while others commensal in the skin microbiome.[39, 40] *C. acnes* has specific culture requirements that prevent growth in routine bacterial culture. *Staphylococcus epidermidis, S. aureus,* and *Malassezia* species have also been identified in acne lesions, although causal relationships remain to be demonstrated.[41-45]

While some *C. acnes* species have developed resistance to antibiotics[46, 47] and certain strains are more strongly associated with acne, routine microbiologic and/or antibiotic susceptibility testing is not indicated for patients with acne since it does not affect management. Patients presenting with eruptive uniform pustules to nodules in periorificial areas, particularly in settings of prolonged tetracycline treatment, may benefit from lesion culture to diagnose Gram-negative folliculitis. Treatment with isotretinoin or another antibiotic may be required. Microbiologic testing may also be considered for patients presenting with monomorphic truncal papules and pustules to diagnose pityrosporum folliculitis.

Androgens, such as testosterone and dehydroepiandrosterone sulfate, have central roles in the pathogenesis of acne. The association between acne severity and androgen levels remains unclear, with some studies showing positive associations while others showed no associations.[48, 49]

Routine endocrinologic testing is not indicated for most patients with acne. Patients who present with acne and clinical signs or symptoms of hyperandrogenism, such as hirsutism, oligomenorrhea or amenorrhea, androgenic alopecia, infertility, polycystic ovaries, clitoromegaly, and truncal obesity may warrant further endocrine testing for hyperandrogenism. Polycystic ovarian syndrome is a common cause of hyperandrogenism, characterized by ovulatory dysfunction or polycystic ovaries on ultrasonography. Tests for serum total and/or free testosterone, dehydroepiandrosterone sulfate, androstenedione, luteinizing hormone, follicle-stimulating hormone may be considered.[50-54] For women with hyperandrogenism, screening for non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency by 17-hydroxyprogesterone levels may be indicated.[50] Serum growth hormone, insulin-like growth factor, sex hormone-binding globulin, free androgen index, lipid panel, insulin, prolactin, estrogen, and progesterone may also be abnormal in some patients with severe acne.[51, 54-57] Patients with abnormal endocrine testing or in whom there is a persistent concern for underlying endocrine disorder should be evaluated by an endocrinologist.

ACNE MANAGEMENT

Treatment options available for acne include topical therapies (available over the counter or as prescriptions), systemic antibiotics, hormonal agents, oral isotretinoin, physical modalities, complementary and alternative medicine, and dietary and environmental interventions. Given the diversity of treatment options for acne, shared-decision making is important to individualize acne care based on the potential treatment benefits and risks, the severity, extent, and region of acne involvement, treatment costs, patient preferences, and other factors (**Figure I**).

TOPICAL THERAPIES

Topical therapies are the mainstay of acne treatment: they may be used for acne initial treatment and maintenance as monotherapy (except topical antibiotics) or used in combination with other topical or oral agents. Commonly used topical therapies include topical retinoids, benzoyl peroxide (BP),

antibiotics, clascoterone, salicylic acid, and azelaic acid. When managing acne with topical therapies, multimodal therapy combining multiple mechanisms of actions is recommended as a good practice statement to optimize efficacy and to reduce the risk of antibiotic resistance.

Topical retinoids

Topical retinoids are vitamin A derivatives and serve as the cornerstone of acne treatment since they are comedolytic and anti-inflammatory, improve dyspigmentation, and enable maintenance of acne clearance. Four types of topical retinoids are FDA-approved for acne treatment in the US, including topical tretinoin,[58] adapalene,[59] tazarotene,[60, 61] and trifarotene.[62] Each retinoid binds to a different set of retinoic acid receptors and confers modest differences in activity, tolerability and efficacy.

We recommend topical retinoids for acne treatment based on moderate certainty evidence from 20 studies (**Table III** and e-Table 12).[59, 62-78] Compared to vehicle at 12 weeks, a greater proportion of patients treated with topical retinoids achieved IGA success in 4 RCT (RR, 1.57 [1.21, 2.04]).[59, 63-65] Topical retinoid use may be limited by side effects, including increased risk of burning sensation, dryness, erythema, exfoliation, peeling, and pain. Treatment-emergent adverse events leading to discontinuation at 12 weeks were low (1.4%) in 3 RCT.[63, 76, 78] Existing comparative effectiveness data do not suggest superiority of one topical retinoid against another, with efficacy and tolerability differing by specific concentrations and formulations.[72, 79-82] Irritation may be particularly common at higher concentrations, which may be mitigated by reduced frequency of use and concurrent emollients use.[83-86] Some tretinoin formulations should be applied in the evening due to its photolabile nature and should not be applied with BP to avoid oxidation and inactivation; topical tretinoin microsphere formulations, adapalene, and tazarotene lack similar restrictions. Topical retinoids may cause photosensitivity; concurrent daily sunscreen use can reduce sunburn risks. Adapalene 0.1% gel is available over the counter while other topical retinoids are available by prescription only.

Benzoyl Peroxide

BP is an over-the-counter topical antimicrobial agent that releases free oxygen radicals and is mildly comedolytic.[87, 88] We recommend BP for acne treatment based on moderate certainty evidence from 8 studies (**Table III** and **e-Table 13**).[63, 64, 89-94] Compared to vehicle at 12 weeks, a greater proportion of patients treated with BP achieved IGA success in 3 RCT (RR, 2.70 [1.10, 6.65]).[63, 64, 89] Greater reductions in both inflammatory (mean difference [MD] in the percentage change from baseline, -22.13% [-42.53%, -1.72%]) and noninflammatory (MD, -17.05% [-22.96%, -11.14%]) lesion counts were seen in BP versus vehicle at 12 weeks in 3 RCT.[63, 90, 93] BP use is limited by concentration and formulation-dependent burning sensation, stinging, dryness, erythema, pain, peeling, irritation, fabric staining and bleaching, and uncommon contact allergy. Lower BP concentrations and water-based and wash-off formulations may be better tolerated.[95, 96] No *C. acnes* resistance to BP has been reported.

Topical Antibiotics

Topical antibiotics (including erythromycin, clindamycin, minocycline, and dapsone) treat acne through both antibacterial and anti-inflammatory effects.[97] We recommend topical antibiotics for acne treatment based on moderate certainty evidence from 14 studies (**Table III** and **e-Table 14**).[65, 75, 90, 92, 93, 98-105] Compared to vehicle at 12 weeks, a greater proportion of patients treated with topical antibiotics achieved IGA success in 3 RCT (RR, 1.49 [1.28, 1.73]).[65, 100, 101]

A greater reduction in inflammatory was seen in BP versus vehicle at 12 weeks in 8 RCT (MD in the percentage change from baseline, -10.86% [-18.81%, -2.91%]),[75, 90, 93, 98-101, 105] but the difference in reduction in noninflammatory lesion counts between the two groups was not statistically significant at 12 weeks in 7 RCT (-3.33% [-7.90%, 1.24%]).[75, 90, 93, 98-101] Notably, topical antibiotic monotherapy is not recommended due to concern for antibiotic resistance. Combining topical antibiotics with BP enhances efficacy and may prevent antibiotic resistance development. Concurrent topical application of BP with either dapsone or sulfacetamide causes an orange-brown skin discoloration, which can be washed off; thus BP should be used at a different time of day than topical dapsone.[106] Glucose-6-phosphate

dehydrogenase screening is not required prior to starting topical dapsone. Topical antibiotics are generally well tolerated; there have been rare case reports describing diarrhea or *Clostridium difficile*-related colitis associated with topical clindamycin use.[107, 108]

Fixed-dose topical combinations

Fixed-dose topical combinations of BP, retinoids, or antibiotics facilitate treatment regimen adherence.[109] We recommend fixed-dose topical combinations of BP and topical retinoid, BP and topical antibiotic, and topical retinoid and topical antibiotic for acne treatment based on moderate certainty evidence from 7 [63, 64, 110-114], 9 [90, 92, 93, 112, 115-119], and 3 [65, 75, 112] studies, respectively (**Table III** and **e-Tables 15-23**). Compared to vehicle at 12 weeks, a greater proportion of patients treated with combined BP and topical retinoid achieved IGA success in 3 RCT (RR, 2.19 [1.77, 2.72]).[63, 64, 110] Greater reductions in both inflammatory (MD in the percentage change from baseline, -37.34% [-72.49%, -2.18%]) and noninflammatory (MD, -20.47% [-26.31, -14.62]) lesion counts were seen in combined BP and topical antibiotic versus vehicle at 12 weeks in 4 RCT.[90, 93, 112, 116] Concomitant BP use is recommended with combined topical retinoid and topical antibiotic to prevent the development of antibiotic resistance. Potential adverse effect profiles of the fixed-dose combinations generally reflect those of the individual agents in summation. Some fixed-dose combination products may be less expensive than prescribing their individual components separately.

Clascoterone

Clascoterone is a topical anti-androgen that directly binds the androgen receptor and inhibits androgen-mediated lipid and inflammatory cytokine synthesis from sebocytes.[120] We conditionally recommend clascoterone for acne treatment based on high certainty evidence from 2 studies (**Table III** and **e-Table 24**) and based on Work Group discussions related to treatment access and cost.

Compared to vehicle at 12 weeks, a greater proportion of patients treated with clascoterone achieved IGA success in 2 RCT (RR, 2.08 [1.39, 3.11]).[121] Despite high certainty of benefits over risks based on clinical trial evidence, the Work Group voted on a conditional recommendation due to concerns

about the high current cost of clascoterone treatment that may impact equitable acne treatment access. This conditional recommendation may be revised in the future pending changes in treatment cost and access.

Salicylic acid

Salicylic acid is a topical comedolytic agent that is available over the counter, with concentration ranging in 0.5%-2%. We conditionally recommend salicylic acid for acne treatment based on moderate certainty evidence from 1 RCT, showing a 25% greater reduction in inflammatory lesions, 11% greater reduction in open comedones, and no difference in closed comedones with 0.5% salicylic acid use compared to vehicle at 12 weeks (**Table III** and **e-Table 25**).[122] Chemical peels using salicylic acid 10%-30% are separately discussed in the physical modalities section.

Azelaic acid

Azelaic acid is a topical comedolytic, antibacterial, and anti-inflammatory agent, which may be particularly helpful for patients with sensitive skin or darker skin types due to its lightening effect on dyspigmentation.[123-125] We conditionally recommend topical azelaic acid for acne treatment based on moderate certainty evidence from 3 RCT (**Table III** and **e-Table 26**).[123, 124, 126] In one RCT of 92 patients, 28% more patients receiving azelaic acid 20% cream twice daily achieved 50-100% reduction in total lesion count compared to vehicle at 3 months.[124]

Considerations in topical therapies

In patients who are pregnant, the risk of fetal harm from topical azelaic acid, BP, erythromycin, and clindamycin are not expected based on limited expected systemic absorption.[127, 128] Salicylic acid can be used in pregnancy if the area of exposure and duration of therapy is limited; use for large areas or under occlusion are not recommended due to the potential for systemic absorption.[127] There is no data on the safety of topical dapsone and clascoterone during pregnancy or lactation. Tazarotene is contraindicated in pregnancy based on animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption. No human studies have established causal relationships between the use

of topical retinoids with birth defects; nevertheless, topical therapies other than topical retinoids are preferred during pregnancy. Topical minocycline is not recommended during pregnancy or lactation.

Salicylic acid is available over-the-counter. FDA-approved acne treatment indication for fixed-dose combination BP 2.5%/adapalene 1% gel, tretinoin 0.1%/BP 3% cream, tretinoin 0.05% lotion, trifarotene 0.005% cream, dapsone 5% gel, and minocycline 4% foam for age 9 years and above; and most other topical retinoids, antibiotics, clascoterone, and azelaic acid for age 12 years and above.

Available evidence is insufficient to develop a recommendation on the use of topical glycolic acid, sulfur, sodium sulfacetamide, and resorcinol for acne treatment or to make recommendations that compare topical BP, retinoids, antibiotics, and their combinations directly against each other (**e-Tables 27-35**).

SYSTEMIC ANTIBIOTICS

Systemic antibiotics have been used extensively to treat acne, typically moderate to severe acne. Oral tetracycline-class antibiotics, including doxycycline, minocycline, and sarecycline, are commonly used. Tetracycline-class antibiotics exhibit antibiotic properties by binding the 16S ribosomal RNA of the bacterial ribosome 30S subunit to inhibit protein synthesis, as well as anti-inflammatory properties by inhibiting neutrophil chemotaxis and matrix metalloproteinases and down-regulating inflammatory cytokines.[129] Notably, tetracycline-class antibiotics are contraindicated in pregnancy, lactation, and childhood below age 9 years during tooth development, since repeated exposure may cause permanent teeth enamel hypoplasia or discoloration.

Limiting the use of systemic antibiotics when possible is recommended as a good practice statement to reduce the development of antibiotic resistance and other antibiotic-associated complications. In 2021, dermatologists prescribed more oral antibiotics per clinician than all other specialties, with the majority of antibiotics used for acne treatment.[130, 131] In addition to concerns about antibiotic resistance, oral tetracycline-class antibiotic use has been associated with inflammatory bowel disease (IBD),[132] pharyngitis,[133] *Clostridium difficile* infection,[134, 135] and *Candida* vulvovaginitis. Outpatient antibiotic

stewardship promotes appropriate antibiotic use in which patients receive the *right* dose of the *right* antibiotic at the *right* time for the *right* duration. The Center for Disease Control and Prevention recommend outpatient antibiotic stewardship programs to include 1) commitment to optimizing antibiotic prescribing and patient safety, 2) implementation action for stewardship policy or practice, 3) tracking prescribing practices through clinician feedback or self-assessment, and 4) access to educational resources and expertise. When treating acne with systemic antibiotics, we recommend concomitant use of BP and other topical therapies as a good practice statement to decrease risk of antibiotic resistance and to limit the duration of systemic antibiotic exposure. Oral antibiotics should not be used as monotherapy for acne treatment. Systemic antibiotic use should also be limited to the shortest duration possible, typically no more than 3-4 months, as recommended by international guidelines.[3, 136, 137] For patients who have inadequate response or contraindications to non-antibiotic therapies and may require longer courses of systemic antibiotics, consistent follow up and re-evaluation should limit systemic antibiotic use to the shortest duration and should maintain treatment endpoints with concurrent topical therapies during and after systemic antibiotic treatment.[138-142]

Doxycycline

We recommend doxycycline for acne treatment based on moderate certainty evidence from 5 studies (**Table III** and e-Table 36).[132, 143-146] Compared to vehicle at 4 months, a greater proportion of patients treated with doxycycline achieved IGA success in 2 RCT (RR, 1.80 [1.17, 2.77]).[144, 145] Treatment withdrawal due to adverse effects was more common with doxycycline compared to placebo in 3 trials (1.3% vs. 0.3%; RR, 2.25 [0.38, 13.21]).[143-145] Doxycycline may cause gastrointestinal disturbances (15.7% vs. 5.9%; RR, 2.56 [1.05, 6.25]),[143-145] including nausea, vomiting, and diarrhea; esophagitis, phototoxicity; and rarely intracranial hypertension. Taking doxycycline with food and adequate fluids in the upright position may reduce gastrointestinal side effects. Low-dose doxycycline (20mg twice daily or 40mg extended release daily) has demonstrated efficacy in patients with moderate

inflammatory acne,[143] but there remains insufficient evidence comparing oral doxycycline at different dosages directly.[147]

We conditionally recommend doxycycline over azithromycin for acne treatment based on low certainty evidence from 4 studies (**Table III** and e-Table 37).[148-151] A greater reduction in total lesion counts was seen in doxycycline versus azithromycin at 12 weeks (MD in the change from baseline, -6.0 [-11.63, -0.37] in 1 RCT.[148] Azithromycin is a broad-spectrum macrolide antibiotic that covers respiratory and other infections; increasing azithromycin use could increase antibiotic resistance.

Minocycline

We conditionally recommend minocycline for acne treatment based on moderate certainty evidence from 5 studies and based on Work Group discussions related to uncommon potential treatment adverse effects (**Table III** and e-Table 38).[132, 152-155] Compared to vehicle at 12 weeks, a greater proportion of patients treated with minocycline achieved IGA success in 2 RCT (RR, 1.82 [1.28, 2.57]).[152-154] Adverse effects requiring treatment cessation were higher with minocycline compared to placebo in 2 RCT (9.1% vs. 1.0%; RR, 6.23 [1.20, 32.99]).[153, 155] Oral minocycline confers similar common adverse effects as doxycycline. Despite moderate certainty of benefits over risks based on clinical trial evidence, the Work Group voted on a conditional recommendation due to concerns about rare potential adverse effects of minocycline, which include vertigo, autoimmune hepatitis, skin hyperpigmentation, drug-induced lupus, and hypersensitivity syndrome. As there is insufficient evidence comparing doxycycline and minocycline directly, the potential risks and benefits of each treatment option should be considered (e-Table 39). Moreover, oral minocycline monotherapy is not superior to topical BP 5% or erythromycin 2%/BP 5% in mild to moderate acne in one RCT (e-Tables 40-42).[156] Available evidence is insufficient to develop a recommendation on the use of long-term minocycline monotherapy or in combination with tazarotene as maintenance therapy beyond 3-4 months over tazarotene gel alone (e-Table 43).[139]

Sarecycline

We conditionally recommend sarecycline for acne treatment based on high certainty evidence from 3 studies and based on Work Group discussions related to treatment access and cost (**Table III** and e-Table 44).[157-159] Sarecycline is a narrow-spectrum tetracycline-class antibiotic, and compared to vehicle at 12 weeks, a greater proportion of patients treated with sarecycline achieved IGA success in 2 RCT (22.3% vs. 13.0%; RR, 1.73 [1.23, 2.44]).[157-159] Sarecycline is dosed by weight at 1.5mg/kg and is generally well tolerated with low incidence of gastrointestinal, photosensitivity, and Candida infection side effects. Despite high certainty of benefits over risks based on clinical trial evidence, the Work Group voted on a conditional recommendation due to concerns about the high current cost of sarecycline treatment that may impact equitable acne treatment access. This conditional recommendation may be revised in the future pending changes in treatment cost and access.

Considerations in systemic antibiotics

Oral doxycycline, minocycline, and sarecycline are FDA-approved for the management of acne. In patients who are pregnant or lactating, tetracycline-class antibiotics should be avoided due to potential for permanent teeth discoloration and bone growth inhibition in the fetus or nursing infant. The 2016 AAD acne guidelines discussed the limited use of oral erythromycin and azithromycin for pregnant persons and on the restricted use of trimethoprim-sulfamethoxazole or trimethoprim for patients unable to tolerate tetracyclines.[3] Available evidence is insufficient to develop a recommendation on the use of oral azithromycin or trimethoprim/sulfamethoxazole for acne treatment (e-Tables 45-48). In addition, TMP-SMX may be associated with severe adverse reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis and acute respiratory failure. These antibiotics are also indicated for community-acquired infections, such as pneumonia and urinary tract infections, and broad use for acne should be discouraged to avoid selection of antibiotic-resistant bacteria. Available evidence is also insufficient to make recommendations that compare systemic antibiotics directly against each other or against topical therapies (e-Tables 49-53).

HORMONAL AGENTS

Combined oral contraceptives

Combined oral contraceptives (COC) contain combinations of estrogen and progestin. COC prevent ovulation and pregnancy by inhibiting gonadotropin-releasing hormone, follicle stimulating hormone, and luteinizing hormone. COC treat acne through their overall anti-androgenic properties, which decrease ovarian androgen production, increase sex hormone-binding globulin, and reduce free testosterone that would otherwise activate the androgen receptor. COC reduce 5α-reductase activity and block the androgen receptor.[160-163]

Ethinyl estradiol (EE) is the most common estrogen component in COC, with daily doses typically ranging from 10-50μg. Progestins are synthesized progesterone analogues and are historically categorized by generations. First, second, and third generation progestins are derived from testosterone and have androgenic potential if used alone. Examples of first-generation oral progestins include norethindrone and ethynodiol diacetate; second-generation include levonorgestrel and norgestrel; and third generation include norgestimate and desogestrel, which are considered less androgenic than prior generations. Progestin-only oral contraceptive pills, intramuscular injections, intrauterine devices, or subcutaneous implants may worsen acne.[164, 165] Fourth generation progestins include oral drospirenone and dienogest. Drospirenone is a spironolactone analogue not derived from testosterone and has anti-androgenic properties. Combined with estrogen, all COC yield net anti-androgenic properties.[161, 166] Four COC are FDA-approved for treatment of acne in women who desire oral contraception, including norgestimate/EE, norethindrone acetate/EE/ferrous fumarate, drospirenone/EE, and drospirenone/EE/levomefolate. All COC are currently available in generic forms in the US.

We conditionally recommend COC for acne treatment based on moderate certainty evidence from 10 studies [167-176] and variability in patient values and preferences related to contraception (Table III and **e-Table 54**). Data on all COC formulations with acne outcomes, regardless of specific approved indication for acne treatment, were pooled and compared against placebo. Compared to vehicle at the end of cycle 6,

a greater proportion of patients treated with COC achieved IGA success in 3 RCT (RR, 1.45 [1.06, 1.97]).[167-169] Greater reductions in both inflammatory (MD in the percentage change from baseline, -15.81% [-20.44%, -11.17%]) and noninflammatory (MD, -19.45% [-29.9, -9.0]) lesion counts were seen in COC versus vehicle at the end of cycle 6 in 9 RCT[167-175] and 6 RCT[168-171, 173, 174], respectively. High dropout rates of 25%-35% across multiple RCT may in part reflect variability in patient preferences regarding COC continuation. Current data show no consistent difference in acne responses based on COC formulations or dosages and do not support the superiority of one COC over another for acne treatment (**e-Table 56 - 61**).[177-183] Reports of any adverse effects (54.0% vs. 50.1%; RR, 1.15 [1.07, 1.24]) and treatment withdrawal due to adverse effects (5.1% vs. 2.9%; 1.86 [1.32, 2.62]) are more common with COC than with placebo. COC for acne treatment is not limited to patients with acne affecting the jawline or with premenstrual flares, hirsutism, or hyperandrogenism. Clinicians should counsel patients about expected time to acne improvement with COC, usually notable within 3-6 months, and may consider combining COC with other acne therapies early in treatment course to accelerate treatment response.

Obtaining a comprehensive medical history and measuring blood pressure are important before prescribing COC.[184] Clinicians may be reasonably certain that a patient who has no symptoms or signs of pregnancy and who meets specific criteria (e.g., who presents within 7 days after the start of normal menses or who have not had sexual intercourse since the start of last normal menses) is not pregnant.[185] Urine pregnancy tests may also be considered.[185] COC access may be expanded using patient eligibility self-screening tools.[186] Pelvic and breast examination, cervical cancer screening, and sexually transmitted infection screening are not required prior to COC initiation.[186] Recommendations for contraceptive selection for patients with specific characteristics or medical conditions are found in the US Medical Eligibility Criteria for Contraceptive Use, 2016, which is available as a mobile application to facilitate use in clinical settings.[187] Absolute and relative contraindications to COC are summarized in **Table IV**.[187] Discussions weighing potential benefits and risks of COC may differ depending on its indication: if a COC is indicated to prevent pregnancy, its risks and benefits should be contextualized against those of an

unintended pregnancy; if a COC is indicated exclusively for acne treatment, its risks and benefits should be compared against those of acne.

Potential adverse effects of COC include venous thromboembolism (VTE), myocardial infarction (MI), stroke, breast cancer, cervical cancer, among others. Typical use of EE with daily dose below 50μg is associated with lower VTE risks compared to historical use of EE with daily doses above 50μg, which are no longer available in the US; existing data have not shown significant effect of further EE dose reductions below 50μg on VTE risks.[186, 188] The absolute risk of VTE associated with COC use is small compared to the risk of VTE in pregnancy.[186, 188] Estimated VTE incidence per 10,000 person-years are estimated at approximately 1-5 in non-pregnant women who do not use COC, 3-9 in COC users, 10 in drospirenone-containing COC users, 5-20 in pregnancy, and 40-65 in the 12-week postpartum period.[186, 188] COC use is associated with a small increases in MI and stroke risks, particularly in patients above age 35 who smoke tobacco or patients who have hypertension, diabetes mellitus, or migraines. While cardiovascular events are important safety concerns, they are uncommon in reproductive-aged patients, in which a small relative risk increase still represents an overall low absolute risk.[161, 162, 189] COC have been associated with small increases in breast cancer and cervical cancer risks and decreases in endometrial, ovarian, and colorectal cancer risks in systematic reviews.[190-194] A long-term cohort study of 46,022 women in the United Kingdom showed an overall neutral balance between short- and long-term cancer risks and benefits in past COC users after 30 years of follow up.[192]

COC confers benefits beyond contraception and acne treatment, including regulating menstrual cycles, induction of amenorrhea, prevention of menstrual migraines, and treatment of conditions such as dysmenorrhea, hirsutism, menorrhagia, endometriosis-associated pelvic pain, premenstrual syndrome, among others.[195] Due to numerous potential benefits, risks, and variability in patient values and preferences, patient-centered contraceptive counseling that prioritize patients' values, preferences, and lived experiences in the shared decision-making of initiation or discontinuation of contraceptive methods is critical.[196] To help all patients achieve reproductive goals, the American College of Obstetricians and Gynecologists recommends intentional application of a reproductive justice framework that acknowledges

historical devaluation of reproductive desires of people of color and other marginalized individuals and conscious and unconscious clinician bias in contraceptive counseling .[196]

COC may be combined with other oral or topical acne medications, including tetracycline antibiotics and spironolactone. Tetracycline-class antibiotics have not been shown to reduce COC effectiveness.[162, 189, 197, 198] Among anti-infectives, rifampin and griseofulvin have demonstrably reduced COC effectiveness.[199] Concomitant use of spironolactone and drospirenone did not increase serum potassium or adverse effects requiring treatment discontinuation.[200, 201] COC is FDA-approved for female patients above age 14 years (drospirenone/EE, drosperinone/EE/levomefolate) or 15 years (norgestimate/EE, norethindrone/EE/ferrous fumarate). A new type of COC with drospirenone/estetrol was approved by the FDA for contraception in 2021;[202] its use for acne was not evaluated in the current guidelines.

Spironolactone

Spironolactone is an aldosterone receptor antagonist that decreases testosterone production and competitively inhibits testosterone and dihydrotestosterone binding to androgen receptors in the skin.[203-206] Spironolactone may also inhibit 5α-reductase and increase steroid-hormone binding globulin.[207,208] Spironolactone is not FDA-approved for the treatment of acne.

We conditionally recommend spironolactone for acne treatment based on moderate certainty evidence from 8 studies (**Table III** and **e-Table 55**).[209-216] Compared to placebo combined with BP 2.5% alone at 12 weeks, a greater proportion of patients treated with spironolactone 50mg daily combined with BP 2.5% achieved IGA success in a small RCT of 40 patients (75.0% vs. 30.0%; RR, 2.50 [1.22, 5.11]).[209] Compared to vehicle at 12 weeks, a greater proportion of patients treated with spironolactone at daily doses ranging from 50-200mg had improvement in patient global assessment in two small RCT of 58 patients (77.4% vs. 22.25; RR, 3.60 [1.75, 7.42]).[210, 211] A cohort study comparing acne patients starting treatment with spironolactone to those starting treatment with oral tetracycline-class antibiotics found similar rates of treatment effectiveness, as assessed by treatment switching, between the two

groups.[217] Menstrual irregularities were commonly reported (40.6% vs. 0%; RR, 10.89 [1.54, 77.08]),[209, 210] may be dose-dependent,[218] and are less common among those using COC.[219] Common side effects also include diuresis, breast tenderness, breast enlargement, gynecomastia, fatigue, headache, and dizziness.[220] Although spironolactone 50-100mg/day showed a greater improvement in IGA at 12 weeks as well as acne-specific quality of life and patient global assessment at 24 weeks compared with placebo in a recent RCT of 410 patients, [221] it was published after the literature search was finalized for the current guidelines."

The Work Group remarked that potassium monitoring is of low usefulness without risk factors for hyperkalemia (e.g., older age, medical co-morbidities, medications) based on very low certainty observational studies. [209-216] No significant changes in serum electrolytes were seen in 2 small RCT of spironolactone for acne treatment.[209, 210] In a large cohort study of 108,547 patients with acne who received spironolactone for ≥30 days, 0.22% received a hyperkalemia diagnosis and 0.03% discontinued spironolactone within 30 days after hyperkalemia diagnosis. A 4-year retrospective cohort study reported 6 cases of hyperkalemia during 291 patient-years of follow up. A retrospective review of 974 women aged 18-45 years receiving spironolactone 50-200mg daily for acne showed that 15 (0.8%) of the 1802 associated potassium measurements exceeded 5.0 mmol/L; all patients with hyperkalemia were asymptomatic and continued spironolactone treatment.[214] In a cohort study of 139 male and female Japanese patients who received spironolactone for acne, with daily dose taper from 200mg to 50mg over 20 weeks, all 25 patients in the subset who received potassium monitoring had normal potassium levels in 32 weeks of follow up.[215] In a cohort study of 124 healthy women with baseline normal serum potassium level, 3 (2.4%) patients aged 42-47 years had incident hyperkalemia upon follow up.[216] Potassium monitoring should be considered in older patients; patients with medical co-morbidities such as hypertension, diabetes mellitus, chronic kidney disease, among others; and patients taking medications affecting renal, adrenal, and hepatic function, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, digoxin, among others. Avoiding a diet high in potassium should be considered.[222]

Spironolactone should not be used in pregnancy. Spironolactone crosses the placenta and exposure in utero in animal studies may cause feminization of a male fetus. Human data are based on limited case reports, with 5 cases resulting in normal male genital development and 1 case of ambiguous genitalia in a newborn of a mother treated with spironolactone until week 5 of gestation.[223] Concurrent COC use is often indicated in treating acne with spironolactone.

Spironolactone carries a warning on tumorigenicity based on chronic toxicity studies in rats that were exposed to up to 150 times human doses of spironolactone or its metabolites. A systematic review of 7 studies of 4.5 million individuals showed no statistically significant association between spironolactone use in men and women above age 18 years and risks of breast cancer (risk ratio [RR] 1.04; 95% CI 0.86-1.22), ovarian cancer (1.52; 0.84-2.20), bladder cancer (0.89; 0.71-1.07); kidney cancer (0.96; 0.85-1.07), gastric cancer (1.02; 0.80-1.24), or esophageal cancer (1.09; 0.91-1.27) based on low to very low certainty of evidence.[224] Spironolactone use is associated with decreased prostate cancer risk (0.79; 0.68-0.90) compared to non-users based on very low certainty of evidence.[224]

Intralesional corticosteroid

Intralesional corticosteroid therapy has been used as an adjuvant therapy for acne. Although there is limited clinical trial data evaluating intralesional corticosteroid injection for acne, in a small RCT of 9 patients, most acne cysts injected with triamcinolone resolved within 3-7 days of the treatment, and those injected with triamcinolone resolved faster than those with saline control.[225] In addition, intralesional corticosteroid injections are effective for a variety of other inflammatory skin conditions such as granuloma annulare, hidradenitis suppurativa, inflamed epidermal cysts, and keloids.[226-232] Together, these characteristics indirectly imply that intralesional corticosteroid injection can be a useful treatment option; therefore, WG issued a good practice statement for intralesional corticosteroid injection use as an adjuvant therapy in patients with larger acne papules or nodules (**Table III**). Intralesional corticosteroid injections should be used judiciously for patients who are at risk of acne scarring and/or for rapid improvement in inflammation and pain. Localized skin atrophy, systemic absorption of steroids, and

possible adrenal suppression may occur.[294] Using a lower concentration and volume of corticosteroid (e.g. triamcinolone 2.5-5 mg/ml) can minimize the risks of local corticosteroid adverse events.[233]

Considerations in hormonal agents

Available evidence is insufficient to develop a recommendation on the use of oral corticosteroids, flutamide, or metformin for acne treatment (e-Table 62- 68). The 2016 AAD acne guidelines discussed the temporary use of oral corticosteroids for patients with severe inflammatory acne while starting standard acne treatment and low-dose oral corticosteroids for patients with adrenal hyperandrogenism.[3] Prednisone 0.5-1mg/kg/day has been used to treat acne fulminans, isotretinoin-induced acne fuminans and to prevent isotretinoin-induced acne flares in at-risk patients.[234, 235] However, long-term adverse effects of oral corticosteroids prohibit their use as a primary acne treatment.

ISOTRETINOIN

Oral isotretinoin, or 13-*cis*-retinoic acid, is the only FDA-approved treatment for severe recalcitrant nodular acne vulgaris since 1982. While the exact mechanism of action is unknown, isotretinoin reduces the size and secretion of sebaceous glands, decreases surface and ductal level of sebum-dependent *C. acnes* indirectly, inhibits comedogenesis by normalizing keratinocyte keratinization, and possesses anti-inflammatory properties.[236]

Despite the remarkable effectiveness of isotretinoin observed in routine dermatology practice, clinical trial data regarding its efficacy are limited and of low quality. In a RCT of 33 patients with treatment-resistant cystic and conglobate acne, mean number of cystic lesions decreased by 17% and 33% at 1 and 2 months of isotretinoin treatment, but increased by 33% and 58% at 1 and 2 months of placebo (e-Table 69).[237] Moreover, 13 of 17 patients receiving placebo switched to isotretinoin due to acne worsening.[237] Earlier dose-response studies showed a significant improvement across all dosages (0.1, 0.5, and 1 mg/kg/day).[238-240] In a RCT of 925 patients comparing standard isotretinoin with lidose isotretinoin, 81.0% of patients treated with standard isotretinoin experienced a 90% reduction in lesion count and 88.9% of patients treated with standard isotretinoin achieved treatment success after 20 weeks

of treatment.[241] In another RCT of 60 patients, low-dose isotretinoin (5mg daily) group had fewer total lesions compared to those in vehicle group after 16 weeks of treatment (MD in total lesion counts, -5.4 [-8.91, -1.89]).[242] Many global acne experts have agreed that isotretinoin is the most appropriate treatment option for those with severe or scarring acne.[136, 137, 243-248] Together, these characteristics indirectly imply the excellent efficacy of isotretinoin; therefore, WG issued a good practice statement for isotretinoin use in patients with severe acne or in patients who have failed standard treatment with oral or topical therapy (**Table III**). The Work Group remarked that patients with acne who present with acne-related psychosocial burden and/or scarring should be considered candidates for isotretinoin treatment. Isotretinoin has been extensively used to treat mild to moderate acne that is refractory to other topical and oral therapies or that relapses quickly after discontinuation of oral antibiotics.[249-254] Common adverse effects associated with isotretinoin involve the mucocutaneous, musculoskeletal and ophthalmic systems and generally resolve following isotretinoin discontinuation with standard treatment courses.[3]

Laboratory monitoring during isotretinoin treatment should include liver function tests, fasting lipid panel, and pregnancy test for patients with pregnancy potential and should not include complete blood count monitoring. While significant heterogeneity exist among study definitions, data from 5 isotretinoin cohort studies estimated that risks of abnormal liver function tests above reference limits ranged from 0.8%-10.4%, with 0.9%-4.7% requiring treatment discontinuation (**e-Table 70**).[255-259] Data from 6 isotretinoin cohort studies estimated that the risks of abnormal triglycerides ranged from 7.1%-39.0% and abnormal cholesterol levels ranged from 6.8%-27.2% (**e-Table 71**).[255-260] Data from 2 isotretinoin cohort studies estimated the risk of mild normocytic anemia as 0.4%, abnormal platelet level at 1.2-2.9%, and abnormal white blood cell count at 7.0-10.8% (**e-Table 72**).[258, 259] No grade 3 or greater abnormalities in the complete blood count was observed.[259] Prior meta-analyses of 26 studies showed that the proportion of patients with laboratory abnormalities was low.[261] A recent Delphi consensus study of 22 acne experts reached agreement on checking alanine aminotransferase and triglycerides prior to initiation and at peak isotretinoin dose and on not checking complete blood count, low-density lipoprotein or high-density lipoprotein.[262] Data on laboratory monitoring in patients treated with isotretinoin have

been critically appraised, with little evidence to support the benefit of laboratory monitoring to detect adverse events.[263]

For persons with pregnancy potential, pregnancy prevention is mandatory with isotretinoin treatment. After introduction of isotretinoin in the US in 1982, there were hundreds of reports of isotretinoin-exposed pregnancies that resulted in fetal congenital malformations.[264] iPLEDGE is the current FDA-mandated Risk Evaluation and Mitigation Strategy aimed to prevent isotretinoin exposure in pregnancy. All patients receiving isotretinoin are required to enroll in and adhere to iPLEDGE. Recent iPLEDGE modification in 2021 categorized patients into 2 gender-neutral categories: patients who cannot become pregnant, per iPLEDGE definition, include a patient who has had a hysterectomy and/or bilateral oophorectomy, a patient who is post-menopausal, or a patient who was born with male reproductive organs. Patients who can become pregnant must adhere to complete abstinence or use 2 specified contraceptive methods at least 1 month before, during, and 1 month after isotretinoin treatment. Since the iPLEDGE implementation, approximately 150 isotretinoin-exposed pregnancies continue to occur in the US annually due to non-adherence with contraceptive requirements.[265, 266] Among sexually active patients who reported non-adherence, 29% did not comply with consistent condom use and 39% missed 1 or more contraceptive pills in the previous month.[266] Patients with pregnancy potential receiving isotretinoin should be carefully counseled regarding various contraceptive methods that are available and the specific requirements of the iPLEDGE system at each clinic visit. Long-acting reversible contraceptives, including intrauterine devices and contraceptive implants, should be considered as the primary contraceptive method whenever clinically appropriate since they have higher effectiveness than COC and condoms in reducing the risk of unintended pregnancy and do not depend on ongoing patient efforts.[267]

Population-based studies have not identified increased risk of neuropsychiatric conditions or IBD in patients with acne undergoing isotretinoin treatment (**e-Table 69**). Available low certainty evidence from 7 observational studies with substantial heterogeneity do not support a significant association between isotretinoin use and IBD incidence, including ulcerative colitis and Crohn's disease.[268-274] The overall RR of IBD between isotretinoin-exposed and unexposed groups is estimated at 1.13 (95% CI,

0.89, 1.43).[268-274] Neuropsychiatric adverse effects, including changes in mood, depression, anxiety, suicidal ideation and completed suicide have been sporadically reported in patients receiving isotretinoin, including with positive challenge/dechallenge, suggesting a potential causal association.[275, 276] However, available low certainty evidence from 4 observational studies with substantial heterogeneity do not support a significant association between isotretinoin use and neuropsychiatric adverse effect incidence.[277-280] The overall RR of adverse neuropsychiatric adverse effects between isotretinoin-exposed and unexposed group is estimated at 0.88 (95% CI 0.77-1.00).[277-280] Multiple studies indicate that isotretinoin may improve quality of life and decrease symptoms of anxiety and depression in patients with moderate to severe acne, which could reduce overall risks of neuropsychiatric adverse events at a population level.[281-283] However, given high prevalence of depression, anxiety and suicidal ideation/suicide in the general population, and especially the adolescent population who may be candidates for isotretinoin therapy, clinicians should monitor for depression, anxiety, suicidal ideation/suicidality, and other neuropsychiatric adverse effects and individualize therapeutic decisions based on individual differences in response to isotretinoin. Notably, the US Preventive Service Task Force recommends screening for depression in adults[284] and in adolescents aged 12-18 years[285] and recommends screening for anxiety in adolescents aged 8-18 years[286], regardless of exposure to isotretinoin, each with Grade B recommendations that concludes with moderate certainty that such screening yields moderate net benefits. The Patient Health Questionnaire-2 and Patient Health Questionnaire-9 have been proposed as efficient and validated instruments for depression screening with isotretinoin treatment.[287]

We conditionally recommend daily dosing over intermittent dosing of isotretinoin based on low certainty evidence from 3 RCT (e-Table 73).[250, 251, 253] Greater reductions in global acne grading system score (MD, -1.75 [-3.38, -0.12]), inflammatory lesion counts (MD, -3.87 [-5.57, -2.17]), and non-inflammatory lesion counts (MD, -4.53 [-6.89, -2.17]) were seen in daily dosing (0.5-0.7mg/kg daily) versus intermittent dosing of isotretinoin (0.5-0.7mg/kg daily for 1week out of every 4 weeks) at 24

weeks in an RCT of 33 patients.[253] Withdrawal due to adverse effects were more common with daily dosing than intermittent dosing (6.7% vs. 0%).[253]

We conditionally recommend either standard isotretinoin or lidose-isotretinoin based on high certainty evidence from 1 study (e-Table 74).[241] Standard isotretinoin has better bioavailability when taken with a high fat meal, whereas the bioavailability of lidose isotretinoin is less affected by whether it is taken with food. In a RCT of 782 patients, lidose-isotretinoin showed non-inferiority in reducing facial and truncal nodular lesions and in the proportion of patients achieving ≥90% reduction of total lesions at 20 weeks (76.9% vs. 81.0%; RR, 0.95 [0.88, 1.02]).[241] No significant differences in adverse effects or treatment withdrawal was noted.[241] Both formulations are available as branded generic prescriptions in the US.

Additional potential adverse effects, such as cardiovascular risk, bone mineralization, scarring, and *S. aureus* colonization, were addressed in the 2016 acne guidelines. Expert consensus from the American Society of Dermatologic Surgery concluded that there is insufficient evidence to justify delaying treatment with superficial chemical peels and nonablative lasers, including hair removal lasers and lights, vascular lasers, and nonablative fractional devices for patients currently receiving or recently received isotretinoin.[288] Full-face dermabrasion, mechanical dermabrasion with rotary devices, and ablative laser treatment of the entire face or non-facial regions are not recommended within 6 months of isotretinoin use due to increased risks of adverse events.[288]

Available evidence is insufficient to directly compare between traditional dosage (0.5mg-1.0mg/kg/day) and low-dosage (<0.5mg/kg/day) isotretinoin regimens, between isotretinoin with systemic antibiotics with or without topical therapies, and between isotretinoin alone and isotretinoin with topical agents (e-Tables 75-80). Although available evidence was insufficient to make a formal recommendation, a few small studies have suggested that low dose regimens may be associated with similar efficacy and rates of relapse compared to higher dose regimens.[239, 253, 289]

PHYSICAL MODALITIES

Physical modalities examined included acne lesion extraction, chemical peels, laser and light-based devices, microneedle radiofrequency devices, and photodynamic therapy. Available evidence is insufficient to develop a recommendation on the use of acne lesion / comedo extraction, chemical peels (including glycolic acid, trichloroacetic acid, salicylic acid, Jessner's solution, or mandelic acid), laser and light-based devices (including 585-595nm pulsed dye laser, neodymium-doped yttrium aluminum garnet laser, 1450 diode laser, potassium titanyl phosphate laser, infrared LED diode, 635-670nm red light, combined 420nm blue light and 660nm red light, 589nm/1319nm laser, or intense pulsed light), microneedle radiofrequency device, or photodynamic therapy with aminolevulinic acid for the treatment of acne (e-Tables 81-159). We conditionally recommend against adding pneumatic broadband light to adapalene 0.3% gel based on low certainty evidence from 1 study (**Table III** and e-Table 160).[290] Adding pneumatic broadband light to adapalene did not reduce acne lesion counts and was associated with risks of hyperpigmentation and purpura.[290] The 1726nm laser was cleared by the FDA for acne treatment in 2022;[291, 292] its evidence was not evaluated in the current guidelines due to lack of a RCT.

COMPLEMENTARY / ALTERNATIVE THERAPIES

Complementary and alternative therapies examined include botanical or plant-derived agents and vitamins. Available evidence is insufficient to develop a recommendation on the use of topical tee tree oil, topical green tea, topical witch hazel, oral pantothenic acid, oral or topical zinc, oral or topical niacinamide for acne treatment (e-Tables 161-173).

DIET

Available evidence is conflicting on low glycemic load diet for acne treatment (e-Tables 174-176). A greater reduction in facial acne score was seen in a low glycemic load diet versus a high glycemic load diet at 8 weeks in an RCT of 45 patients (MD in change from baseline, -0.3 [-0.39, -0.21]).[293] One RCT of 32 Korean patients showed improvement in the Leeds Revised Acne score at 12

weeks in a low glycemic load diet group, but not in vehicle group.[294] A greater reduction in total lesion count was seen in a low glycemic load diet versus a high glycemic load diet at 12 weeks in an RCT of 43 Australian patients (MD in change from baseline, -8.1 [-14.89, -1.31])[295] However, in an RCT of 84 patients, the addition of a low glycemic diet in patients starting BP 2.5% gel did not result in significant differences in acne lesion counts.[296] Available evidence is insufficient to develop a recommendation on the use of low dairy diet, low whey diet, omega-3 fatty acids, and chocolate on acne treatment.

GAPS IN RESEARCH AND STUDY LIMITATIONS

These guidelines identified important evidence gaps on the use of microbiology and endocrinology testing in acne, the use of systemic antibiotics beyond tetracycline-class antibiotics, physical modalities, complementary and alternative therapies, dietary interventions for the treatment of acne, and cost-effectiveness of acne treatments. RCT with long-term follow up and comparative effectiveness research are necessary to examine and compare patient-centered acne treatment outcomes. Increased use of active comparator trials are needed when multiple interventions exist within a treatment class, such as among topical retinoids and topical antibiotics.[297, 298] Additional research is needed on optimizing value of laboratory monitoring for patients receiving spironolactone and isotretinoin. A list of interventions and comparisons of interventions identified, evaluated, and not considered to be viable candidates for recommendation development due to insufficient evidence is available in **e-Table 177**.

Tailoring acne management in diverse populations will require incorporation of diversity, equity, and inclusion efforts in the acne research pipeline. Women, patients of color, and sexual and gender minority patients may be disproportionately affected by acne.[21, 299-301] Many acne RCT specify contraceptive requirements and exclusion criteria related to hormone therapy.[302] To optimize acne care in patients with pregnancy potential and LGBTQ+ patients, future acne research should incorporate ongoing national efforts to collect high-quality information about sex, gender identity, and sexual orientation and to examine real-life acne treatment effects by including patients with variations in contraceptive use and

hormone therapy status.[302-304] Additional research on the safety and efficacy of acne treatments in the context of pregnancy and lactation are required.[127, 305]

Patients with skin of color may disproportionately suffer from acne sequelae, including acne-induced hyperpigmentation and keloidal scarring, which may be under-appreciated or undertreated by clinicians.[300] A systematic review of the treatments of acne-associated hyperpigmentation and scarring fall beyond the scope of these guidelines but is an area of important work. In addition to early treatment of acne, common treatments for acne-induced hyperpigmentation include topical retinoids, azelaic acid, hydroquinone, and physical modalities such as lasers and chemical peels. Common treatments for keloidal scars include topical silicone, intralesional corticosteroids, or lasers. A recent systematic review of 55 studies on acne in skin of color was unable to draw firm conclusions to guide distinct decisions in acne practice in patients with skin of color.[300] Only 4 of 55 studies evaluated acne outcomes in Fitzpatrick skin types IV to VI. The lack of research representation was most notable among Black, African American, and Afro-Caribbean patients. Expanding diversity and inclusion of acne RCT will be critical to examine acne treatment in patients with skin of color.

This guideline is developed based on analysis of the best available data at the time it was conducted. The results of future studies may necessitate revision of current recommendations. Study limitations included the pragmatic decision to limit the literature review to English language, which may have excluded relevant data published in other languages. Due to the large scope of the review using GRADE methodology, the analysis included only RCTs, which may have limited identification of relevant long-term follow-up data.

SUMMARY

Analysis of the evidence from this systematic review based on 9 clinical questions resulted in 18 evidence-based recommendations and 5 good practice statements for the treatment of acne. Strong recommendations are made for benzoyl peroxide, topical retinoids, and topical antibiotics, as well as for oral doxycycline. Oral isotretinoin is strongly recommended for acne that is severe, causing psychosocial

burden or scarring, or failing standard oral or topical therapy. Conditional recommendations are made for topical clascoterone, salicylic acid, azelaic acid, as well as for oral minocycline, sarecycline, combined oral contraceptive pills, and spironolactone. Combining topical therapies with multiple mechanisms of action, limiting systemic antibiotic use, combining systemic antibiotics with topical therapies, and adding intralesional corticosteroid injections for larger acne lesions are recommended as good practice statements (**Table III**).

WORK GROUP MEMBERS' DISCLOSURES

The information below represents the authors' disclosed relationship with industry during guideline development. Authors (listed alphabetically) with relevant conflicts with respect to this guideline are noted with an asterisk*. In accordance with AAD policy, a minimum 51% of Work Group members did not have any relevant conflicts of interest.

Participation in one or more of the listed activities below constitutes a relevant conflict:

- service as a member of a speaker bureau, consultant, advisory board, for pharmaceutical companies on atopic dermatitis or atopic dermatitis drugs in development or FDA-approved.
- sponsored research funding or investigator-initiated studies with partial/full funding from pharmaceutical companies on atopic dermatitis or atopic dermatitis drugs in development or FDA-approved

If a potential conflict was noted, the work group member recused themselves from the discussion and drafting of recommendations pertinent to the topic area of interest. Complete group consensus was obtained for draft recommendations. Areas where complete consensus was not achieved are shown transparently in the guideline.

Rachel V.S. Reynolds, MD, Carol E. Cheng, MD, Kelly Druby, Megha M. Tollefson, MD, and Jung Min Han, PharmD, MS, have no relationships to disclose. Howa Yeung, MD, MS, serves as an investigator for American Acne & Rosacea Society, Department of Veterans Affairs, and National Institutes of Health receiving grants and research funding; as an independent contractor for American Academy of

Dermatology and Journal of the American Medical Association receiving fees; as a speaker/faculty educator for Dermatology Digest receiving honoraria. Fran Cook-Bolden, MD, serves as an advisory board member for AbbVie, Dermavant Sciences, Inc., Galderma Global, Novartis, Ortho Dermatologics, and Pfizer Inc. receiving honoraria; as an investigator for Arcutis Biotherapeutics receiving grant and research funding; as a speaker for Galderma Laboratories, LP, Journey Medical Corporation, and Ortho Dermatologics receiving honoraria; as others for Topix Pharmaceuticals, Inc. receiving other financial benefit. Seemal R. Desai, MD, serves an advisory board member for Foundation for Research & Education of Dermatology receiving fees; as a consultant for AbbVie, Allergan, Inc, Almirall, Amgen, Apogee, Avita, Ballature Beauty, Beiersdorf, Inc., Bristol-Myers Squibb, Candela Corporation, Cassiopea S.p.A., Castle Biosciences, Cutera, Inc., Dermavant Sciences, Dermira, Eli Lilly and Company, EPI Health, Ferndale Laboratories, Inc., Foamix, Galderma Laboratories, LP, Gore Range Capital, Hyphens Pharma, Incyte Corporation, Janssen Pharmaceuticals, Inc, Johnson and Johnson, Leo Pharma Inc., L'Oreal USA Inc., Lyceum Health, Ortho Dermatologics, Pfizer Inc., Revision Skincare, Sanofi/Regeneron, Scientis, Skin Science Advisors, UCB , Verrica Pharmaceuticals Inc., and VYNE Therapeutics receiving fees, honoraria, and/or stock options; as an investigator for AOBiome, LLC, Atacama Therapeutics, Dermavant Sciences, Incyte Corporation, and SkinMedica, Inc. receiving grants and research funding; as a speaker for AbbVie, Dermira, Galderma Laboratories, LP., and Pfizer Inc. receiving fees; as a stockholder for Gore Range Capital; as other role for Medscape receiving fees. Esther E. Freeman, MD, PhD, serves as an investigator for International League of Dermatologic Societies and National Institutes of Health receiving grants and research funding; as an author for UptoDate, Inc. and British Journal of Dermatology, receiving honoraria or salary; as a speaker for Harvard University. Jonette E. Keri, MD, PhD, serves as an advisory board member for Ortho Dermatologics receiving honoraria; as a consultant for Almirall receiving fees; as an investigator for Galderma USA receiving grants and research funding; as a speaker for Foamix Pharmaceuticals Ltd and VYNE Therapeutics receiving honoraria. Linda F. Stein Gold, MD, serves as an advisory board member for AbbVie, Almirall, Aqua, Dermavant Sciences, Foamix, Galderma Laboratories, L.P., GlaxoSmithKline, Incyte Corporation,

La Roche-Posay Laboratorie Pharmaceutique, LEO Pharma, US, Lilly ICOS LLC, Merz Pharmaceuticals, LLC, Pfizer Inc., Promius Pharmaceuticals, Sanofi/Regeneron, Taro Pharm, and Valeant Pharmaceuticals International receiving honoraria; as a consultant for AnaptysBio, BMS, Botanix Pharmaceuticals, Cutera, Inc., Incyte Corporation, Janssen Scientific Affairs, LLC, Sol-Gel Technologies, Taro Pharm, The Acne Store, and UCB receiving honoraria or grants and research funding; as an investigator for AbbVie, Allergan, Inc., AnaptysBio, Galderma Laboratories, L.P., Leo Pharma Inc., Novartis Pharmaceuticals Corp., Pfizer Inc., Topica, and Valeant Pharmaceuticals International receiving grants and research funding; as a speaker for Actavis, Almirall, BMS, Dermira, Pfizer Inc., Sanofi/Regeneron, Sun Pharmaceutical Industries Ltd., and VYNE Therapeutics receiving honoraria. Jerry K. L. Tan, MD, serves as an advisory board member for Abbott Laboratories, Cutera, Inc., Galderma Laboratories, L.P, and Sun Pharmaceutical Industries Ltd receiving honoraria or grants and research funding; as a consultant for Bausch Health, Boots, Galderma Research & Development, LLC, and Loreal Research and Innovation receiving honoraria; as an independent contractor for Norvatis receiving fees; as an investigator for Allergan, AnaptysBio, Cutera, Inc., Eli Lilly and Co., Galderma Laboratories, L.P, Lilly ICOS LLC, Pfizer, and UCB for receiving grants and research funding; as a speaker for Bausch Health, LEO Laboratories Ltd (LEO Pharma), and Vichy Laboratories receiving honoraria. Jonathan S. Weiss, MD, serves as an advisory board member for Bristol-Myers Squibb, Dermavant Sciences, Foamix, Galderma Laboratories, L.P., Incyte Corporation, Novartis, and UCB receiving honoraria; as a consultant for Arcutis, Inc., Biofrontera, Cutera, Inc., Leo Pharma Inc, Ortho Dermatologics, and UCB receiving fees or honoraria; as an investigator for AbbVie, Bausch Health, Biofrontera, Bristol-Myers Squibb, Cutera, Inc., Dermavant Sciences, Foamix, Galderma Laboratories, L.P., LEO Pharma, Mindera, Moberg Pharma North, America LLC, Novartis, Palvella Therapeutics, and Verrica Pharmaceuticals Inc receiving grants and research funding; as a speaker for AbbVie, Arcutis, Inc., Galderma Laboratories, L.P., Ortho Dermatologics, Regeneron, and Sanofi Genzyme receiving honoraria. Peggy A. Wu, MD, serves as others for UptoDate, Inc. receiving honoraria. Andrea L. Zaenglein, MD, serves as a consultant for Church & Dwight Co., Inc. and UCB receiving fees or honoraria; as an investigator for AbbVie, Arcutis

Biotherapeutics, Biofrontera AG, Galderma Laboratories, L.P., and Incyte Corporation receiving grants and research funding. John S. Barbieri, MD, MBA serves as investigator for National Institutes of Health and National Psoriasis Foundation receiving grants and research funding.

ACKNOWLEDGMENT

We thank Peter A. Lio, MD for his contributions to establishing the scope of the acne guideline update and David A. Castillo and Charniel McDaniels for helping with data extraction and full text article procurement.

REFERENCES

1. Lim HW, Collins SAB, Resneck JS, Jr., Bolognia JL, Hodge JA, Rohrer TA et al. The burden of skin disease in the United States. J Am Acad Dermatol 2017;76:958-72 e2.
2. Chen H, Zhang TC, Yin XL, Man JY, Yang XR , Lu M. Magnitude and temporal trend of acne vulgaris burden in 204 countries and territories from 1990 to 2019: an analysis from the Global Burden of Disease Study 2019. Br J Dermatol 2022;186:673-83.
3. Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol 2016;74:945-73 e33.
4. Eichenfield LF, Krakowski AC, Piggott C, Del Rosso J, Baldwin H, Friedlander SF et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics 2013;131 Suppl 3:S163-86.
5. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719-25.
6. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726-35.
7. Guyatt GH, Alonso-Coello P, Schunemann HJ, Djulbegovic B, Nothacker M, Lange S et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol 2016;80:3-7.
8. Eichenfield DZ, Sprague J , Eichenfield LF. Management of Acne Vulgaris: A Review. JAMA 2021;326:2055-67.
9. Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, Margolis DJ et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. J Invest Dermatol 2014;134:1527-34.
10. Bhate K , Williams HC. Epidemiology of acne vulgaris. The British journal of dermatology 2013;168:474-85.
11. Karimkhani C, Dellavalle RP, Coffeng LE, Flohr C, Hay RJ, Langan SM et al. Global Skin Disease Morbidity and Mortality: An Update From the Global Burden of Disease Study 2013. JAMA Dermatol 2017;153:406-12.
12. White GM. Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. Journal of the American Academy of Dermatology 1998;39:S34-7.

13. Fabbrocini G, Cacciapuoti S , Monfrecola G. A Qualitative Investigation of the Impact of Acne on Health-Related Quality of Life (HRQL): Development of a Conceptual Model. Dermatol Ther (Heidelb) 2018;8:85-99.
14. Barbieri JS, Fulton R, Neergaard R, Nelson MN, Barg FK , Margolis DJ. Patient Perspectives on the Lived Experience of Acne and Its Treatment Among Adult Women With Acne: A Qualitative Study. JAMA Dermatol 2021;157:1040-6.
15. Mallon E, Newton JN, Klassen A, Stewart-Brown SL, Ryan TJ , Finlay AY. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. Br J Dermatol 1999;140:672-6.
16. Cresce ND, Davis SA, Huang WW , Feldman SR. The quality of life impact of acne and rosacea compared to other major medical conditions. J Drugs Dermatol 2014;13:692-7.
17. Gupta MA , Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. Br J Dermatol 1998;139:846-50.
18. Magin P, Adams J, Heading G, Pond D , Smith W. Experiences of appearance-related teasing and bullying in skin diseases and their psychological sequelae: results of a qualitative study. Scand J Caring Sci 2008;22:430-6.
19. Ritvo E, Del Rosso JQ, Stillman MA , La Riche C. Psychosocial judgements and perceptions of adolescents with acne vulgaris: A blinded, controlled comparison of adult and peer evaluations. Biopsychosoc Med 2011;5:11.
20. Purvis D, Robinson E, Merry S , Watson P. Acne, anxiety, depression and suicide in teenagers: a cross-sectional survey of New Zealand secondary school students. J Paediatr Child Health 2006;42:793-6.
21. Heng AHS , Chew FT. Systematic review of the epidemiology of acne vulgaris. Sci Rep 2020;10:5754.
22. Layton AM, Whitehouse H, Eady EA, Cowdell F, Warburton KL , Fenton M. Prioritizing treatment outcomes: How people with acne vulgaris decide if their treatment is working. J Evid Based Med 2017;10:163-70.
23. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for Industry. Acne vulgaris: developing drugs for treatment. . Silver Spring, MD2005.
24. O'Brien S, Lewis J , Cunliffe W. The Leeds revised acne grading system. Journal of Dermatological Treatment 1998;9:215-20.
25. Doshi A, Zaheer A , Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. Int J Dermatol 1997;36:416-8.
26. Dreno B, Poli F, Pawin H, Beylot C, Faure M, Chivot M et al. Development and evaluation of a Global Acne Severity Scale (GEA Scale) suitable for France and Europe. J Eur Acad Dermatol Venereol 2011;25:43-8.
27. Tan JK, Tang J, Fung K, Gupta AK, Thomas DR, Sapra S et al. Development and validation of a comprehensive acne severity scale. J Cutan Med Surg 2007;11:211-6.
28. Patel DP, Bernardis E , Yan AC. The patient-centered acne severity scale study. Pediatr Dermatol 2017;34:656-60.
29. Bernardis E, Shou H, Barbieri JS, McMahon PJ, Perman MJ, Rola LA et al. Development and Initial Validation of a Multidimensional Acne Global Grading System Integrating Primary Lesions and Secondary Changes. JAMA Dermatol 2020;156:296-302.
30. Cho SI, Yang JH , Suh DH. Analysis of trends and status of physician-based evaluation methods in acne vulgaris from 2000 to 2019. J Dermatol 2021;48:42-8.
31. Stein Gold L, Tan J , Kircik L. Evolution of Acne Assessments and Impact on Acne Medications: An Evolving, Imperfect Paradigm. J Drugs Dermatol 2016;15:79-86.
32. Tan JK, Jones E, Allen E, Pripotnev S, Raza A , Wolfe B. Evaluation of essential clinical components and features of current acne global grading scales. J Am Acad Dermatol 2013;69:754-61.

33. Tan J, Wolfe B, Weiss J, Stein-Gold L, Bikowski J, Del Rosso J et al. Acne severity grading: determining essential clinical components and features using a Delphi consensus. J Am Acad Dermatol 2012;67:187-93.
34. Gottlieb A, Salame N, Armstrong AW, Merola JF, Parra S, Takeshita J et al. A provider global assessment quality measure for clinical practice for inflammatory skin disorders. J Am Acad Dermatol 2019;80:823-8.
35. Becker M, Wild T , Zouboulis CC. Objective assessment of acne. Clin Dermatol 2017;35:147-55.
36. Chernyshov PV, Zouboulis CC, Tomas-Aragones L, Jemec GB, Manolache L, Tzellos T et al. Quality of life measurement in acne. Position Paper of the European Academy of Dermatology and Venereology Task Forces on Quality of Life and Patient Oriented Outcomes and Acne, Rosacea and Hidradenitis Suppurativa. J Eur Acad Dermatol Venereol 2018;32:194-208.
37. Marron SE, Chernyshov PV , Tomas-Aragones L. Quality-of-Life Research in Acne Vulgaris: Current Status and Future Directions. Am J Clin Dermatol 2019;20:527-38.
38. Hopkins ZH, Thiboutot D, Homsi HA, Perez-Chada LM , Barbieri JS. Patient-Reported Outcome Measures for Health-Related Quality of Life in Patients With Acne Vulgaris: A Systematic Review of Measure Development and Measurement Properties. JAMA Dermatol 2022;158:900-11.
39. Fitz-Gibbon S, Tomida S, Chiu BH, Nguyen L, Du C, Liu M et al. Propionibacterium acnes strain populations in the human skin microbiome associated with acne. The Journal of investigative dermatology 2013;133:2152-60.
40. Miura Y, Ishige I, Soejima N, Suzuki Y, Uchida K, Kawana S 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.
41. Akaza N, Akamatsu H, Numata S, Yamada S, Yagami A, Nakata S et al. Microorganisms inhabiting follicular contents of facial acne are not only Propionibacterium but also Malassezia spp. J Dermatol 2016;43:906-11.
42. Jusuf NK, Putra IB , Sari L. Differences of Microbiomes Found in Non-Inflammatory and Inflammatory Lesions of Acne Vulgaris. Clin Cosmet Investig Dermatol 2020;13:773-80.
43. Dreno B, Martin R, Moyal D, Henley JB, Khammari A , Seité S. Skin microbiome and acne vulgaris: Staphylococcus, a new actor in acne. Exp Dermatol 2017;26:798-803.
44. Kim J, Park T, Kim HJ, An S , Sul WJ. Inferences in microbial structural signatures of acne microbiome and mycobiome. J Microbiol 2021;59:369-75.
45. Numata S, Akamatsu H, Akaza N, Yagami A, Nakata S , Matsunaga K. Analysis of facial skin-resident microbiota in Japanese acne patients. Dermatology (Basel, Switzerland) 2014;228:86-92.
46. Ergin C, Ergin S, Kaleli I, Kaçar N, Sengül M , Erdoğan BS. Nasal antibiotic-resistant Propionibacterium acnes carriage in acne vulgaris patients in Turkey. J Dermatol 2006;33:899-901.
47. Schafer F, Fich F, Lam M, Gárate C, Wozniak A , Garcia P. Antimicrobial susceptibility and genetic characteristics of Propionibacterium acnes isolated from patients with acne. Int J Dermatol 2013;52:418-25.
48. Franik G, Bizoń A, Włoch S, Kowalczyk K, Biernacka-Bartnik A , Madej P. Hormonal and metabolic aspects of acne vulgaris in women with polycystic ovary syndrome. Eur Rev Med Pharmacol Sci 2018;22:4411-8.
49. Kiayani AJ , Rehman FU. Association Of Serum Testosterone And Sex Hormone Binding Globulin Levels In Females With Acne Based On Its Severity. J Ayub Med Coll Abbottabad 2016;28:357-9.
50. Martin KA, Anderson RR, Chang RJ, Ehrmann DA, Lobo RA, Murad MH et al. Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2018;103:1233-57.
51. Seirafi H, Farnaghi F, Vasheghani-Farahani A, Alirezaie NS, Esfahanian F, Firooz A et al. Assessment of androgens in women with adult-onset acne. Int J Dermatol 2007;46:1188-91.
52. Schmidt JB, Lindmaier A , Spona J. Endocrine parameters in acne vulgaris. Endocrinol Exp 1990;24:457-64.

53. Lucky AW, McGuire J, Rosenfield RL, Lucky PA , Rich BH. Plasma androgens in women with acne vulgaris. J Invest Dermatol 1983;81:70-4.
54. Timpatanapong P , Rojanasakul A. Hormonal profiles and prevalence of polycystic ovary syndrome in women with acne. J Dermatol 1997;24:223-9.
55. Arora MK, Seth S , Dayal S. The relationship of lipid profile and menstrual cycle with acne vulgaris. Clin Biochem 2010;43:1415-20.
56. Abulnaja KO. Changes in the hormone and lipid profile of obese adolescent Saudi females with acne vulgaris. Braz J Med Biol Res 2009;42:501-5.
57. Saleh BO. Role of growth hormone and insulin-like growth factor-I in hyperandrogenism and the severity of acne vulgaris in young males. Saudi medical journal 2012;33:1196-200.
58. Tyring SK, Kircik LH, Pariser DM, Guenin E, Bhatt V , Pillai R. Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: Assessment of efficacy and safety in patients aged 9 years and older. Journal of Drugs in Dermatology 2018;17(10):1084-91.
59. Thiboutot D, Pariser DM, Egan N, Flores J, Herndon JH, Jr., Kanof NB et al. Adapalene gel 0.3% for the treatment of acne vulgaris: a multicenter, randomized, double-blind, controlled, phase III trial. J Am Acad Dermatol 2006;54:242-50.
60. Shalita AR, Chalker DK, Griffith RF, Herbert AA, Hickman JG, Maloney JM et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. Cutis 1999;63:349-54.
61. Tanghetti EA, Werschler WP, Lain T, Guenin E, Martin G , Pillai R. Tazarotene 0.045% Lotion for Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris: Results from Two Phase 3 Trials. J Drugs Dermatol 2020;19:70-7.
62. Tan J, Thiboutot D, Popp G, Gooderham M, Lynde C, Del Rosso J et al. Randomized phase 3 evaluation of trifarotene 50 mug/g cream treatment of moderate facial and truncal acne. Journal of the American Academy of Dermatology 2019;80(6):1691-9.
63. Webster GF, Sugarman J, Levy-Hacham O , Toledano O. Microencapsulated Benzoyl Peroxide and Tretinoin for the Treatment of Acne Vulgaris: Results from a Phase 2 Multicenter, Double-Blind, Randomized, Vehicle-Controlled Study. Skinmed 2020;18(6):343-51.
64. Gollnick HP, Draelos Z, Glenn MJ, Rosoph LA, Kaszuba A, Cornelison R et al. Adapalene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients. Br J Dermatol 2009;161:1180-9.
65. Jarratt MT , Brundage T. Efficacy and safety of clindamycin-tretinoin gel versus clindamycin or tretinoin alone in acne vulgaris: a randomized, double-blind, vehicle-controlled study. J Drugs Dermatol 2012;11:318-26.
66. Trifu V, Tiplica GS, Naumescu E, Zalupca L, Moro L , Celasco G. Cortexolone 17alpha-propionate 1% cream, a new potent antiandrogen for topical treatment of acne vulgaris. A pilot randomized, double-blind comparative study vs. placebo and tretinoin 0.05% cream. Br J Dermatol 2011;165:177-83.
67. Baldwin HE, Green LJ, Kircik L, Guenin EP, Forest AL , Pillai R. Tazarotene 0.045% Lotion for Moderate-to-Severe Acne in Male and Female Participants: A Phase II Post-hoc Analysis. J Clin Aesthet Dermatol 2021;14:E53-E60.
68. Lain E, Day D, Harper J , Guenin E. Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris: Impact of Gender and Race on Efficacy and Safety. Journal of drugs in dermatology : JDD 2019;18(11):1128-38.
69. Green LJ, Del Rosso JQ, Tanghetti EA , Guenin E. Tazarotene 0.045% Lotion for Moderate-to-Severe Acne Patients: Pooled Phase 3 Analysis by Age and Sex. Journal of drugs in dermatology : JDD 2021;20(6):608-15.
70. Stein Gold L, Pariser DM , Guenin E. Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate and Severe Acne Vulgaris in Females: Effect of Age on Efficacy and Tolerability. Journal of drugs in dermatology : JDD 2019;18(12):1218-25.

71. Paracha MM, Ullah I, Zahoor H , Kammal K. Efficacy and safety of short term use of 0.1% tazarotene gel in the treatment of mild to moderate acne vulgaris: A randomized-vehicle controlled trial. Journal of Postgraduate Medical Institute 2020;34(2):134-8.
72. Shalita A, Weiss JS, Chalker DK, Ellis CN, Greenspan A, Katz HI 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. Journal of the American Academy of Dermatology 1996;34:482-5.
73. Alirezai M, George SA, Coutts I, Roseeuw DI, Hachem JP, Kerrouche N et al. Daily treatment with adapalene gel 0.1% maintains initial improvement of acne vulgaris previously treated with oral lymecycline. Eur J Dermatol 2007;17:45-51.
74. Lucky AW, Cullenb SI, Jarratt MT , Quigley JW. Comparative efficacy and safety of two 0.025% tretinoin gels: Results from a multicenter, double-blind, parallel study. Journal of the American Academy of Dermatology 1998;38:S17-S23.
75. Glass D, Boorman GC, Stables GI, Cunliffe WJ , Goode K. A placebo-controlled clinical trial to compare a gel containing a combination of isotretinoin (0.05%) and erythromycin (2%) with gels containing isotretinoin (0.05%) or erythromycin (2%) alone in the topical treatment of acne vulgaris. Dermatology (Basel, Switzerland) 1999;199:242-7.
76. Tanghetti EA, Kircik LH, Green LJ, Guenin E, Harris S, Martin G et al. A Phase 2, Multicenter, Double-Blind, Randomized, Vehicle-Controlled Clinical Study to Compare the Safety and Efficacy of a Novel Tazarotene 0.045% Lotion and Tazarotene 0.1% Cream in the Treatment of Moderate-to-Severe Acne Vulgaris. Journal of drugs in dermatology : JDD 2019;18(6):542.
77. Chalker DK, Lesher JL, Smith JG, Klauda HC, Pochi PE, Jacoby WS et al. Efficacy of topical isotretinoin 0.05% gel in acne vulgaris: Results of a multicenter, double-blind investigation. Journal of the American Academy of Dermatology 1987;17:251-4.
78. Harper JC, Roberts WE, Zeichner JA, Guenin E, Bhatt V , Pillai R. Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of safety and tolerability in subgroups. Journal of Dermatological Treatment 2020;31(2):160-7.
79. 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.
80. Kakita L. Tazarotene versus tretinoin or adapalene in the treatment of acne vulgaris. J Am Acad Dermatol 2000;43:S51-4.
81. 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.
82. 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.
83. Pedace FJ , Stoughton R. Topical retinoic acid in acne vulgaris. Br J Dermatol 1971;84:465-9.
84. Christiansen JV, Gadborg E, Ludvigsen K, Meier CH, Norholm A, Pedersen D et al. Topical tretinoin, vitamin A acid (Airol) in acne vulgaris. A controlled clinical trial. Dermatologica 1974;148:82-9.
85. Cunliffe WJ, Caputo R, Dreno B, Forstrom L, Heenen M, Orfanos CE 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:S126-34.
86. Krishnan G. Comparison of two concentrations of tretinoin solution in the topical treatment of acne vulgaris. Practitioner 1976;216:106-9.
87. Cunliffe WJ, Dodman B , Ead R. Benzoyl peroxide in acne. Practitioner 1978;220:479-82.
88. 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. Journal of cutaneous pathology 1974;1:191-200.
89. Kawashima M, Hashimoto H, Alio Saenz AB, Ono M , Yamada M. Is benzoyl peroxide 3% topical gel effective and safe in the treatment of acne vulgaris in Japanese patients? A multicenter, randomized, double-blind, vehicle-controlled, parallel-group study. Journal of Dermatology 2014;41(9):795-801.

90. Eichenfield LF , Alio Saenz AB. Safety and efficacy of clindamycin phosphate 1.2%-benzoyl peroxide 3% fixed-dose combination gel for the treatment of acne vulgaris: a phase 3, multicenter, randomized, double-blind, active- and vehicle-controlled study. J Drugs Dermatol 2011;10:1382-96.
91. Smith EB, Padilla RS, McCabe JM , Becker LE. Benzoyl peroxide lotion (20 percent) in acne. Cutis 1980;25:90-2.
92. Chalker DK, Shalita A, Smith JG , Swann RW. A double-blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. Journal of the American Academy of Dermatology 1983;9:933-6.
93. Lookingbill DP, Chalker DK, Lindholm JS, Katz HI, Kempers SE, Huerter CJ 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. Journal of the American Academy of Dermatology 1997;37:590-5.
94. Hughes BR, Norris JF , Cunliffe WJ. A double-blind evaluation of topical isotretinoin 0.05%, benzoyl peroxide gel 5% and placebo in patients with acne. Clin Exp Dermatol 1992;17:165-8.
95. Fyrand O , Jakobsen HB. Water-based versus alcohol-based benzoyl peroxide preparations in the treatment of acne vulgaris. Dermatologica 1986;172:263-7.
96. 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;25:664-7.
97. 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;82:260-5.
98. Eichenfield LF, Lain T, Frankel EH, Jones TM, Chang-Lin JE, Berk DR et al. Efficacy and safety of once-daily dapsone gel, 7.5% for treatment of adolescents and adults with acne vulgaris: Second of two identically designed, large, multicenter, randomized, vehicle-controlled trials. Journal of Drugs in Dermatology 2016;15(8):962-9.
99. Stein Gold LF, Jarratt MT, Bucko AD, Grekin SK, Berlin JM, Bukhalo M et al. Efficacy and Safety of Once-Daily Dapsone Gel, 7.5% for Treatment of Adolescents and Adults With Acne Vulgaris: First of Two Identically Designed, Large, Multicenter, Randomized, Vehicle-controlled Trials. Journal of Drugs in Dermatology 2016;15(5):553-61.
100. Alexis A, Del Rosso JQ, Desai SR, Downie JB, Draelos ZD, Feser C et al. BPX-01 minocycline topical gel shows promise for the treatment of moderate-tosevere inflammatory acne vulgaris. Journal of Clinical and Aesthetic Dermatology 2018;11(11):25-35.
101. Raoof TJ, Hooper D, Moore A, Zaiac M, Sullivan T, Kircik L et al. Efficacy and safety of a novel topical minocycline foam for the treatment of moderate to severe acne vulgaris: A phase 3 study. Journal of the American Academy of Dermatology 2020;82(4):832-7.
102. Pochi PE, Bagatell FK, Ellis CN, Stoughton RB, Whitmore CG, Saatjian GD et al. Erythromycin 2 percent gel in the treatment of acne vulgaris. Cutis 1988;41:132-6.
103. Dobson RL , Belknap BS. Topical erythromycin solution in acne: Results of a multiclinic trial. Journal of the American Academy of Dermatology 1980;3:478-82.
104. Bernstein JE , Shalita AR. Topically applied erythromycin in inflammatory acne vulgaris. Journal of the American Academy of Dermatology 1980;2:318-21.
105. Lesher JL, Chalker DK, Smith JG, Guenther LC, Ellis CN, Voorhees JJ et al. An evaluation of a 2% erythromycin ointment in the topical therapy of acne vulgaris. Journal of the American Academy of Dermatology 1985;12:526-31.
106. Dubina MI , Fleischer AB, Jr. Interaction of topical sulfacetamide and topical dapsone with benzoyl peroxide. Arch Dermatol 2009;145:1027-9.
107. Becker LE, Bergstresser PR, Whiting DA, Clendenning WE, Dobson RL, Jordan WP et al. Topical clindamycin therapy for acne vulgaris. A cooperative clinical study. Arch Dermatol 1981;117:482-5.
108. Parry MF , Rha CK. Pseudomembranous colitis caused by topical clindamycin phosphate. Arch Dermatol 1986;122:583-4.

109. Yentzer BA, Ade RA, Fountain JM, Clark AR, Taylor SL, Fleischer AB, Jr. et al. Simplifying regimens promotes greater adherence and outcomes with topical acne medications: a randomized controlled trial. Cutis 2010;86:103-8.
110. Dreno B, Bissonnette R, Gagne-Henley A, Barankin B, Lynde C, Kerrouche N et al. Prevention and Reduction of Atrophic Acne Scars with Adapalene 0.3%/Benzoyl Peroxide 2.5% Gel in Subjects with Moderate or Severe Facial Acne: Results of a 6-Month Randomized, Vehicle-Controlled Trial Using Intra-Individual Comparison. American journal of clinical dermatology 2018;19(2):275-86.
111. Weiss J, Gold LS, Leoni M, Rueda MJ, Liu H , Tanghetti E. Customized single-agent therapy management of severe inflammatory acne: A randomized, double-blind, parallel-Group, controlled study of a new treatment - Adapalene 0.3%-benzoyl peroxide 2.5% gel. Journal of Drugs in Dermatology 2015;14(12):1427-35.
112. Stein Gold L, Baldwin H, Kircik LH, Weiss JS, Pariser DM, Callender V et al. Efficacy and Safety of a Fixed-Dose Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne: A Randomized Phase II Study of the First Triple-Combination Drug. American Journal of Clinical Dermatology 2021.
113. Stein Gold L, Weiss J, Rueda MJ, Liu H , Tanghetti E. Moderate and Severe Inflammatory Acne Vulgaris Effectively Treated with Single-Agent Therapy by a New Fixed-Dose Combination Adapalene 0.3 %/Benzoyl Peroxide 2.5 % Gel: A Randomized, Double-Blind, Parallel-Group, Controlled Study. American journal of clinical dermatology 2016;17(3):293-303.
114. Stein Gold L, Werschler WP , Mohawk J. Adapalene/Benzoyl Peroxide Gel 0.3%/2.5%: Effective Acne Therapy Regardless of Age or Gender. 2017;1:582-9.
115. Harper JC. The efficacy and tolerability of a fixed combination clindamycin (1.2%) and benzoyl peroxide (3.75%) aqueous gel in patients with facial acne vulgaris: Gender as a clinically relevant outcome variable. Journal of Drugs in Dermatology 2015;14(4):381-4.
116. 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. Journal of Drugs in Dermatology 2014;13(9):1083-9.
117. Cook-Bolden FE. Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and benzoyl peroxide (3.75%) aqueous gel in moderate or severe adolescent acne vulgaris. Journal of Clinical and Aesthetic Dermatology 2015;8(5):28-32.
118. Gold MH , Korotzer A. Sub-group Analyses from a Trial of a Fixed Combination of Clindamycin Phosphate 1.2% and Benzoyl Peroxide 3.75% Gel for the Treatment of Moderate-to-severe Acne Vulgaris. 2015;1:22-6.
119. Stein Gold L. Efficacy and Tolerability of a Fixed Combination of Clindamycin Phosphate (1.2%) and Benzoyl Peroxide (3.75%) Aqueous Gel in Moderate and Severe Acne Vulgaris Subpopulations. Journal of drugs in dermatology : JDD 2015;14(9):969-74.
120. Rosette C, Agan FJ, Mazzetti A, Moro L , Gerloni M. Cortexolone 17alpha-propionate (Clascoterone) Is a Novel Androgen Receptor Antagonist that Inhibits Production of Lipids and Inflammatory Cytokines from Sebocytes In Vitro. J Drugs Dermatol 2019;18:412-8.
121. Hebert A, Thiboutot D, Stein Gold L, Cartwright M, Gerloni M, Fragasso E et al. Efficacy and Safety of Topical Clascoterone Cream, 1%, for Treatment in Patients with Facial Acne: Two Phase 3 Randomized Clinical Trials. JAMA Dermatology 2020;156(6):621-30.
122. Shalita AR. Treatment of mild and moderate acne vulgaris with salicylic acid in an alcohol-detergent vehicle. Cutis 1981;28:556-8, 61.
123. Cunliffe WJ , Holland KT. Clinical and laboratory studies on treatment with 20% azelaic acid cream for acne. Acta Derm Venereol Suppl (Stockh) 1989;143:31-4.
124. 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;143:35-9.
125. 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;10:586-90.

126. Iraji F, Sadeghinia A, Shahmoradi Z, Siadat AH , Jooya A. Efficacy of topical azelaic acid gel in the treatment of mild-moderate acne vulgaris. Indian J Dermatol Venereol Leprol 2007;73:94-6.
127. Murase JE, Heller MM , Butler DC. Safety of dermatologic medications in pregnancy and lactation: Part I. Pregnancy. J Am Acad Dermatol 2014;70:401 e1-14; quiz 15.
128. Ly S, Kamal K, Manjaly P, Barbieri JS , Mostaghimi A. Treatment of Acne Vulgaris During Pregnancy and Lactation: A Narrative Review. Dermatol Ther (Heidelb) 2023;13:115-30.
129. Perret LJ , Tait CP. Non-antibiotic properties of tetracyclines and their clinical application in dermatology. Australas J Dermatol 2014;55:111-8.
130. Barbieri JS, Bhate K, Hartnett KP, Fleming-Dutra KE , Margolis DJ. Trends in Oral Antibiotic Prescription in Dermatology, 2008 to 2016. JAMA Dermatol 2019;155:290-7.
131. Centers for Disease Control and Prevention. Outpatient Antibiotic Prescriptions — United States, 20212022.
132. 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;105:2610-6.
133. Margolis DJ, Fanelli M, Kupperman E, Papadopoulos M, Metlay JP, Xie SX et al. Association of pharyngitis with oral antibiotic use for the treatment of acne: a cross-sectional and prospective cohort study. Arch Dermatol 2012;148:326-32.
134. Bartlett JG, Chang TW, Gurwith M, Gorbach SL , Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. The New England journal of medicine 1978;298:531-4.
135. Carroll KC , Bartlett JG. Biology of Clostridium difficile: implications for epidemiology and diagnosis. Annual review of microbiology 2011;65:501-21.
136. Nast A, Dréno B, Bettoli V, Bukvic Mokos Z, Degitz K, Dressler C et al. European evidence-based (S3) guideline for the treatment of acne - update 2016 - short version. J Eur Acad Dermatol Venereol 2016;30:1261-8.
137. Oon HH, Wong SN, Aw DCW, Cheong WK, Goh CL , Tan HH. Acne Management Guidelines by the Dermatological Society of Singapore. J Clin Aesthet Dermatol 2019;12:34-50.
138. Gold LS, Cruz A, Eichenfield L, Tan J, Jorizzo J, Kerrouche N 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.
139. Leyden J, Thiboutot DM, Shalita AR, Webster G, Washenik K, Strober BE et al. Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. Arch Dermatol 2006;142:605-12.
140. Tan J, Stein Gold L, Schlessinger J, Brodell R, Jones T, Cruz A et al. Short-term combination therapy and long-term relapse prevention in the treatment of severe acne vulgaris. J Drugs Dermatol 2012;11:174-80.
141. Thiboutot DM, Shalita AR, Yamauchi PS, Dawson C, Kerrouche N, Arsonnaud S 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.
142. Moon SH, Roh HS, Kim YH, Kim JE, Ko JY , Ro YS. Antibiotic resistance of microbial strains isolated from Korean acne patients. J Dermatol 2012;39:833-7.
143. Skidmore R, Kovach R, Walker C, Thomas J, Bradshaw M, Leyden J et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. Arch Dermatol 2003;139:459-64.
144. Leyden JJ, Bruce S, Lee CS, Ling M, Sheth PB, Stewart DM 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;12:658-63.
145. Moore A, Ling M, Bucko A, Manna V , Rueda MJ. Efficacy and Safety of Subantimicrobial Dose, Modified-Release Doxycycline 40 mg Versus Doxycycline 100 mg Versus Placebo for the treatment of

Inflammatory Lesions in Moderate and Severe Acne: A Randomized, Double-Blinded, Controlled Study. J Drugs Dermatol 2015;14:581-6.
146. Plewig G, Petrozzi JW , Berendes U. Double-blind study of doxycycline in acne vulgaris. Arch Dermatol 1970;101:435-8.
147. 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;7:1149-52.
148. 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.
149. Babaeinejad S, Khodaeiani E , Fouladi RF. Comparison of therapeutic effects of oral doxycycline and azithromycin in patients with moderate acne vulgaris: what is the role of age? Journal of dermatological treatment 2011;22:206-10.
150. 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;26:64-7.
151. Kus S, Yucelten D , Aytug A. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of acne vulgaris. Clin Exp Dermatol 2005;30:215-20.
152. Fleischer AB, Jr., Dinehart S, Stough D, Plott RT, Solodyn Phase 2 Study G , Solodyn Phase 3 Study G. Safety and efficacy of a new extended-release formulation of minocycline. Cutis 2006;78:21-31.
153. Stewart DM, Torok HM, Weiss JS, Plott RT , Solodyn Phase 2 Study G. Dose-ranging efficacy of new once-daily extended-release minocycline for acne vulgaris. Cutis 2006;78:11-20.
154. Leyden J, Bergfeld W, Drake L, Dunlap F, Goldman MP, Gottlieb AB et al. A systemic type 15-reductase inhibitor is ineffective in the treatment of acne vulgaris. Journal of the American Academy of Dermatology 2004;50:443-7.
155. Hersle K , Gisslen H. Minocycline in acne vulgaris: a double-blind study. Curr Ther Res Clin Exp 1976;19:339-42.
156. Ozolins M, Eady EA, Avery AJ, Cunliffe WJ, Po AL, O'Neill C et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. Lancet 2004;364:2188-95.
157. Moore A, Green LJ, Bruce S, Sadick N, Tschen E, Werschler P et al. Once-Daily Oral Sarecycline 1.5 mg/kg/day Is Effective for Moderate to Severe Acne Vulgaris: Results from Two Identically Designed, Phase 3, Randomized, Double-Blind Clinical Trials. J Drugs Dermatol 2018;17:987-96.
158. Leyden JJ, Sniukiene V, Berk DR , Kaoukhov A. Efficacy and Safety of Sarecycline, a Novel, Once-Daily, Narrow Spectrum Antibiotic for the Treatment of Moderate to Severe Facial Acne Vulgaris: Results of a Phase 2, Dose-Ranging Study. J Drugs Dermatol 2018;17:333-8.
159. Pariser DM, Green LJ, Lain EL, Schmitz C, Chinigo AS, McNamee B et al. Safety and Tolerability of Sarecycline for the Treatment of Acne Vulgaris: Results from a Phase III, Multicenter, Open-Label Study and a Phase I Phototoxicity Study. J Clin Aesthet Dermatol 2019;12:E53-e62.
160. Arowojolu AO, Gallo MF, Lopez LM , Grimes DA. Combined oral contraceptive pills for treatment of acne. The Cochrane database of systematic reviews 2012;6:CD004425.
161. Arrington EA, Patel NS, Gerancher K , Feldman SR. Combined oral contraceptives for the treatment of acne: a practical guide. Cutis 2012;90:83-90.
162. Harper JC. Should dermatologists prescribe hormonal contraceptives for acne? Dermatologic therapy 2009;22:452-7.
163. Rabe T, Kowald A, Ortmann J , Rehberger-Schneider S. Inhibition of skin 5 alpha-reductase by oral contraceptive progestins in vitro. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2000;14:223-30.
164. Barbieri JS, Mitra N, Margolis DJ, Harper CC, Mostaghimi A , Abuabara K. Influence of Contraception Class on Incidence and Severity of Acne Vulgaris. Obstetrics and gynecology 2020;135:1306-12.
165. Lortscher D, Admani S, Satur N , Eichenfield LF. Hormonal Contraceptives and Acne: A Retrospective Analysis of 2147 Patients. J Drugs Dermatol 2016;15:670-4.

166. Davtyan C. Four Generations of Progestins in Oral Contraceptives. UCLA Comprehensive Health Program2012.
167. Maloney JM, Dietze P, Jr., Watson D, Niknian M, Lee-Rugh S, Sampson-Landers C 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;112:773-81.
168. Thiboutot D, Archer DF, Lemay A, Washenik K, Roberts J , Harrison DD. A randomized, controlled trial of a low-dose contraceptive containing 20 microg of ethinyl estradiol and 100 microg of levonorgestrel for acne treatment. Fertil Steril 2001;76:461-8.
169. Leyden J, Shalita A, Hordinsky M, Swinyer L, Stanczyk FZ , Weber ME. Efficacy of a low-dose oral contraceptive containing 20 microg of ethinyl estradiol and 100 microg of levonorgestrel for the treatment of moderate acne: A randomized, placebo-controlled trial. J Am Acad Dermatol 2002;47:399-409.
170. Redmond GP, Olson WH, Lippman JS, Kafrissen ME, Jones TM , Jorizzo JL. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial. Obstet Gynecol 1997;89:615-22.
171. Lucky AW, Henderson TA, Olson WH, Robisch DM, Lebwohl M , Swinyer LJ. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. J Am Acad Dermatol 1997;37:746-54.
172. Palombo-Kinne E, Schellschmidt I, Schumacher U , Graser T. Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate. Contraception 2009;79:282-9.
173. Maloney JM Arbit D, Flack M, McLaughlin-Miley C, Sevilla C, Derman R. . Use of low-dose oral contraceptive containing norethindrone acetate and ethinyl estradiol in the treatment of moderate acne vulgaris. . Clinical Journal of Women's Health 2001;1:123-31.
174. Koltun W, Lucky AW, Thiboutot D, Niknian M, Sampson-Landers C, Korner P 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;77:249-56.
175. 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.
176. Katz HI, Kempers S, Akin MD, Dunlap F, Whiting D , Norbart TC. Effect of a desogestrel-containing oral contraceptive on the skin. Eur J Contracept Reprod Health Care 2000;5:248-55.
177. Kelly S, Davies E, Fearns S, McKinnon C, Carter R, Gerlinger C et al. Effects of oral contraceptives containing ethinylestradiol with either drospirenone or levonorgestrel on various parameters associated with well-being in healthy women: a randomized, single-blind, parallel-group, multicentre study. Clin Drug Investig 2010;30:325-36.
178. Palatsi R, Hirvensalo E, Liukko P, Malmiharju T, Mattila L, Riihiluoma P et al. Serum total and unbound testosterone and sex hormone binding globulin (SHBG) in female acne patients treated with two different oral contraceptives. Acta Derm Venereol 1984;64:517-23.
179. Rosen MP, Breitkopf DM , Nagamani M. A randomized controlled trial of second- versus third-generation oral contraceptives in the treatment of acne vulgaris. Am J Obstet Gynecol 2003;188:1158-60.
180. Winkler UH, Ferguson H , Mulders JA. Cycle control, quality of life and acne with two low-dose oral contraceptives containing 20 microg ethinylestradiol. Contraception 2004;69:469-76.
181. 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;90:535-41.
182. Thorneycroft H, Gollnick H , Schellschmidt I. Superiority of a combined contraceptive containing drospirenone to a triphasic preparation containing norgestimate in acne treatment. Cutis 2004;74:123-30.

183. Thorneycroft IH, Stanczyk FZ, Bradshaw KD, Ballagh SA, Nichols M , Weber ME. Effect of low-dose oral contraceptives on androgenic markers and acne. Contraception 1999;60:255-62.
184. 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;285:2232-9.
185. Curtis KM, Jatlaoui TC, Tepper NK, Zapata LB, Horton LG, Jamieson DJ et al. U.S. Selected Practice Recommendations for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65:1-66.
186. ACOG Committee Opinion Number 540. Risk of Venous Thromboembolism Among Users of Drospirenone-Containing Oral Contraceptive Pills: American College of Obstetricians and Gynecologists; 2012.
187. Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65:1-103.
188. Food and Drug Administration. Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints2011.
189. Katsambas AD , Dessinioti C. Hormonal therapy for acne: why not as first line therapy? facts and controversies. Clin Dermatol 2010;28:17-23.
190. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2013;22:1931-43.
191. Havrilesky LJ, Moorman PG, Lowery WJ, Gierisch JM, Coeytaux RR, Urrutia RP et al. Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. Obstetrics and gynecology 2013;122:139-47.
192. Iversen L, Sivasubramaniam S, Lee AJ, Fielding S , Hannaford PC. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. American journal of obstetrics and gynecology 2017;216:580 e1- e9.
193. International Collaboration of Epidemiological Studies of Cervical C, Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S 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;370:1609-21.
194. Roura E, Travier N, Waterboer T, de Sanjose S, Bosch FX, Pawlita M et al. The Influence of Hormonal Factors on the Risk of Developing Cervical Cancer and Pre-Cancer: Results from the EPIC Cohort. PLoS One 2016;11:e0147029.
195. ACOG Practice Bulletin No. 110: noncontraceptive uses of hormonal contraceptives. Obstetrics and gynecology 2010;115:206-18.
196. American College of Obstetricians and Gynecologists' Committee on Health Care for Underserved Women, Contraceptive Equity Expert Work Group, and Committee on Ethics. Patient-Centered Contraceptive Counseling: ACOG Committee Statement Number 1. Obstetrics and gynecology 2022;139:350-3.
197. Helms SE, Bredle DL, Zajic J, Jarjoura D, Brodell RT , Krishnarao I. Oral contraceptive failure rates and oral antibiotics. J Am Acad Dermatol 1997;36:705-10.
198. London BM , Lookingbill DP. Frequency of pregnancy in acne patients taking oral antibiotics and oral contraceptives. Arch Dermatol 1994;130:392-3.
199. Bulletins-Gynecology ACoP. ACOG practice bulletin. No. 73: Use of hormonal contraception in women with coexisting medical conditions. Obstetrics and gynecology 2006;107:1453-72.
200. 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;58:60-2.
201. Bird ST, Pepe SR, Etminan M, Liu X, Brophy JM , Delaney JA. The association between drospirenone and hyperkalemia: a comparative-safety study. BMC Clin Pharmacol 2011;11:23.

202. Creinin MD, Westhoff CL, Bouchard C, Chen MJ, Jensen JT, Kaunitz AM et al. Estetrol-drospirenone combination oral contraceptive: North American phase 3 efficacy and safety results. Contraception 2021;104:222-8.
203. Boisselle A, Dionne FT , Tremblay RR. Interaction of spironolactone with rat skin androgen receptor. Canadian journal of biochemistry 1979;57:1042-6.
204. Menard RH, Martin HF, Stripp B, Gillette JR , Bartter FC. Spironolactone and cytochrome P-450: impairment of steroid hydroxylation in the adrenal cortex. Life sciences 1974;15:1639-48.
205. 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;94:1628-36.
206. 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;46:338-44.
207. 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 pharmacology : the official journal of the Skin Pharmacology Society 1994;7:33-40.
208. Serafini PC, Catalino J , Lobo RA. The effect of spironolactone on genital skin 5 alpha-reductase activity. Journal of steroid biochemistry 1985;23:191-4.
209. Patiyasikunt M, Chancheewa B, Asawanonda P, Noppakun N , Kumtornrut C. Efficacy and tolerability of low-dose spironolactone and topical benzoyl peroxide in adult female acne: A randomized, double-blind, placebo-controlled trial. J Dermatol 2020;47:1411-6.
210. Goodfellow A, Alaghband-Zadeh J, Carter G, Cream JJ, Holland S, Scully J et al. Oral spironolactone improves acne vulgaris and reduces sebum excretion. Br J Dermatol 1984;111:209-14.
211. Muhlemann MF, Carter GD, Cream JJ , Wise P. Oral spironolactone: an effective treatment for acne vulgaris in women. Br J Dermatol 1986;115:227-32.
212. Barbieri JS, Margolis DJ , Mostaghimi A. Temporal Trends and Clinician Variability in Potassium Monitoring of Healthy Young Women Treated for Acne With Spironolactone. JAMA Dermatol 2021;157:296-300.
213. Grandhi R , Alikhan A. Spironolactone for the Treatment of Acne: A 4-Year Retrospective Study. Dermatology (Basel, Switzerland) 2017;233:141-4.
214. Plovanich M, Weng QY , Mostaghimi A. Low Usefulness of Potassium Monitoring Among Healthy Young Women Taking Spironolactone for Acne. JAMA Dermatol 2015;151:941-4.
215. Sato K, Matsumoto D, Iizuka F, Aiba-Kojima E, Watanabe-Ono A, Suga H et al. Anti-androgenic therapy using oral spironolactone for acne vulgaris in Asians. Aesthetic Plast Surg 2006;30:689-94.
216. Thiede RM, Rastogi S, Nardone B, Sadowsky LM, Rangel SM, West DP et al. Hyperkalemia in women with acne exposed to oral spironolactone: A retrospective study from the RADAR (Research on Adverse Drug Events and Reports) program. Int J Womens Dermatol 2019;5:155-7.
217. Barbieri JS, Choi JK, Mitra N , Margolis DJ. Frequency of Treatment Switching for Spironolactone Compared to Oral Tetracycline-Class Antibiotics for Women With Acne: A Retrospective Cohort Study 2010-2016. J Drugs Dermatol 2018;17:632-8.
218. Layton AM, Eady EA, Whitehouse H, Del Rosso JQ, Fedorowicz Z , van Zuuren EJ. Oral Spironolactone for Acne Vulgaris in Adult Females: A Hybrid Systematic Review. Am J Clin Dermatol 2017;18:169-91.
219. Garg V, Choi JK, James WD , Barbieri JS. Long-term use of spironolactone for acne in women: A case series of 403 patients. J Am Acad Dermatol 2021;84:1348-55.
220. Shaw JC , White LE. Long-term safety of spironolactone in acne: results of an 8-year followup study. Journal of cutaneous medicine and surgery 2002;6:541-5.
221. Santer M, Lawrence M, Renz S, Eminton Z, Stuart B, Sach TH et al. Effectiveness of spironolactone for women with acne vulgaris (SAFA) in England and Wales: pragmatic, multicentre, phase 3, double blind, randomised controlled trial. BMJ (Clinical research ed) 2023;381:e074349.

222. Zeichner JA. Evaluating and treating the adult female patient with acne. J Drugs Dermatol 2013;12:1416-27.
223. Liszewski W , Boull C. Lack of evidence for feminization of males exposed to spironolactone in utero: A systematic review. J Am Acad Dermatol 2019;80:1147-8.
224. Bommareddy K, Hamade H, Lopez-Olivo MA, Wehner M, Tosh T , Barbieri JS. Association of Spironolactone Use With Risk of Cancer: A Systematic Review and Meta-analysis. JAMA Dermatol 2022;158:275-82.
225. Levine RM , Rasmussen JE. Intralesional corticosteroids in the treatment of nodulocystic acne. Archives of dermatology 1983;119:480-1.
226. Alikhan A, Sayed C, Alavi A, Alhusayen R, Brassard A, Burkhart C et al. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part I: Diagnosis, evaluation, and the use of complementary and procedural management. J Am Acad Dermatol 2019;81:76-90.
227. Hochman B, Locali RF, Matsuoka PK , Ferreira LM. Intralesional triamcinolone acetonide for keloid treatment: a systematic review. Aesthetic Plast Surg 2008;32:705-9.
228. Muneuchi G, Suzuki S, Onodera M, Ito O, Hata Y , Igawa HH. Long-term outcome of intralesional injection of triamcinolone acetonide for the treatment of keloid scars in Asian patients. Scand J Plast Reconstr Surg Hand Surg 2006;40:111-6.
229. Riis PT, Boer J, Prens EP, Saunte DM, Deckers IE, Emtestam L et al. Intralesional triamcinolone for flares of hidradenitis suppurativa (HS): A case series. J Am Acad Dermatol 2016;75:1151-5.
230. Seif-El-Nasr H , El-Komy HM. Granuloma annulare. Report of a case treated successfully by intralesional triamcinolone injection. J Egypt Med Assoc 1962;45:105-6.
231. Sparrow G , Abell E. Granuloma annulare and necrobiosis lipoidica treated by jet injector. Br J Dermatol 1975;93:85-9.
232. Zouboulis CC, Bechara FG, Dickinson-Blok JL, Gulliver W, Horváth B, Hughes R et al. Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimization - systematic review and recommendations from the HS ALLIANCE working group. J Eur Acad Dermatol Venereol 2019;33:19-31.
233. Gallagher T, Taliercio M, Nia JK, Hashim PW , Zeichner JA. Dermatologist Use of Intralesional Triamcinolone in the Treatment of Acne. J Clin Aesthet Dermatol 2020;13:41-3.
234. Jansen T , Plewig G. Acne fulminans. Int J Dermatol 1998;37:254-7.
235. Karvonen SL. Acne fulminans: report of clinical findings and treatment of twenty-four patients. J Am Acad Dermatol 1993;28:572-9.
236. Villani A, Nastro F, Di Vico F, Fabbrocini G, Annunziata MC , Genco L. Oral isotretinoin for acne: a complete overview. Expert Opin Drug Saf 2022;21:1027-37.
237. Peck GL, Olsen TG, Butkus D, Pandya M, Arnaud-Battandier J, Gross EG et al. Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. J Am Acad Dermatol 1982;6:735-45.
238. Farrell LN, Strauss JS , Stranieri AM. The treatment of severe cystic acne with 13-cis-retinoic acid: Evaluation of sebum production and the clinical response in a multiple-dose trial. Journal of the American Academy of Dermatology 1980;3:602-11.
239. 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;107:583-90.
240. Strauss JS, Rapini RP, Shalita AR, Konecky E, Pochi PE, Comite H et al. Isotretinoin therapy for acne: Results of a multicenter dose-response study. Journal of the American Academy of Dermatology 1984;10:490-6.
241. Webster GF, Leyden JJ , Gross JA. Results of a Phase III, double-blind, randomized, parallel-group, non-inferiority study evaluating the safety and efficacy of isotretinoin-Lidose in patients with severe recalcitrant nodular acne. J Drugs Dermatol 2014;13:665-70.
242. Rademaker M, Wishart JM , Birchall NM. Isotretinoin 5 mg daily for low-grade adult acne vulgaris--a placebo-controlled, randomized double-blind study. J Eur Acad Dermatol Venereol 2014;28:747-54.

243. Asai Y, Baibergenova A, Dutil M, Humphrey S, Hull P, Lynde C et al. Management of acne: Canadian clinical practice guideline. Cmaj 2016;188:118-26.
244. Gollnick HP, Bettoli V, Lambert J, Araviiskaia E, Binic I, Dessinioti C et al. A consensus-based practical and daily guide for the treatment of acne patients. J Eur Acad Dermatol Venereol 2016;30:1480-90.
245. Le Cleach L, Lebrun-Vignes B, Bachelot A, Beer F, Berger P, Brugère S et al. Guidelines for the management of acne: recommendations from a French multidisciplinary group. Br J Dermatol 2017;177:908-13.
246. Thiboutot DM, Dréno B, Abanmi A, Alexis AF, Araviiskaia E, Barona Cabal MI et al. Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol 2018;78:S1-S23.e1.
247. Gómez-Flores M, Poletti-Vázquez DE, García-Hidalgo L, Fierro-Arias L, Herz-Ruelas M, Garza-Gómez J et al. [Second joint position paper: Use of isotretinoin in severe acne]. Rev Med Inst Mex Seguro Soc 2019;56:441-6.
248. Bagatin E, Costa CS, Rocha M, Picosse FR, Kamamoto CSL, Pirmez R et al. Consensus on the use of oral isotretinoin in dermatology - Brazilian Society of Dermatology. An Bras Dermatol 2020;95 Suppl 1:19-38.
249. Kassem B, Ismail M , Hassan F. Evaluation of the efficacy and relapse rates of treatment protocols for moderate acne using isotretinoin based on the global acne grading system: Randomized, controlled, comparative study. Dermatologic therapy 2022;35:e15974.
250. Agarwal US, Besarwal RK , Bhola K. Oral isotretinoin in different dose regimens for acne vulgaris: a randomized comparative trial. Indian journal of dermatology, venereology and leprology 2011;77:688-94.
251. 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. Archives of dermatological research 2007;299:467-73.
252. 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;25:1094-8.
253. Lee JW, Yoo KH, Park KY, Han TY, Li K, Seo SJ 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;164:1369-75.
254. Kaymak Y , Ilter N. The effectiveness of intermittent isotretinoin treatment in mild or moderate acne. J Eur Acad Dermatol Venereol 2006;20:1256-60.
255. Amichai B, Shemer A , Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol 2006;54:644-6.
256. Kızılyel O, Metin MS, Elmas Ö F, Çayır Y , Aktaş A. Effects of oral isotretinoin on lipids and liver enzymes in acne patients. Cutis 2014;94:234-8.
257. Ghaffarpour G, Mazloomi S, Soltani-Arabshahi R , Seyed KS. Oral isotretinoin for acne, adjusting treatment according to patient's response. J Drugs Dermatol 2006;5:878-82.
258. Evaristo L , Bagatin E. Use of oral isotretinoin to treat acne in the public system: a hospital-based retrospective cohort. Sao Paulo Med J 2019;137:363-8.
259. Barbieri JS, Shin DB, Wang S, Margolis DJ , Takeshita J. The clinical utility of laboratory monitoring during isotretinoin therapy for acne and changes to monitoring practices over time. J Am Acad Dermatol 2020;82:72-9.
260. Yap FB. Safety and efficacy of fixed-dose 10 mg daily isotretinoin treatment for acne vulgaris in Malaysia. J Cosmet Dermatol 2017;16:348-52.
261. Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G , Kirby JS. Laboratory Monitoring During Isotretinoin Therapy for Acne: A Systematic Review and Meta-analysis. JAMA Dermatol 2016;152:35-44.

262. Xia E, Han J, Faletsky A, Baldwin H, Beleznay K, Bettoli V et al. Isotretinoin Laboratory Monitoring in Acne Treatment: A Delphi Consensus Study. JAMA Dermatol 2022;158:942-8.
263. Affleck A, Jackson D, Williams HC, Chavez P , Albrecht J. Is routine laboratory testing in healthy young patients taking isotretinoin necessary: a critically appraised topic. Br J Dermatol 2022;187:857-65.
264. Dai WS, LaBraico JM , Stern RS. Epidemiology of isotretinoin exposure during pregnancy. J Am Acad Dermatol 1992;26:599-606.
265. Shin J, Cheetham TC, Wong L, Niu F, Kass E, Yoshinaga MA et al. The impact of the iPLEDGE program on isotretinoin fetal exposure in an integrated health care system. Journal of the American Academy of Dermatology 2011;65:1117-25.
266. Collins MK, Moreau JF, Opel D, Swan J, Prevost N, Hastings M et al. Compliance with pregnancy prevention measures during isotretinoin therapy. J Am Acad Dermatol 2014;70:55-9.
267. Committee on Practice Bulletins-Gynecology L-ARCWG. Practice Bulletin No. 186: Long-Acting Reversible Contraception: Implants and Intrauterine Devices. Obstetrics and gynecology 2017;130:e251-e69.
268. 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. The Journal of investigative dermatology 2013;133:907-12.
269. 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;104:2774-8.
270. 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;105:1986-93.
271. 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;149:216-20.
272. Racine A, Cuerq A, Bijon A, Ricordeau P, Weill A, Allemand H et al. Isotretinoin and risk of inflammatory bowel disease: a French nationwide study. Am J Gastroenterol 2014;109:563-9.
273. Wright S, Strunk A , Garg A. Risk of new-onset inflammatory bowel disease among patients with acne vulgaris exposed to isotretinoin. J Am Acad Dermatol 2021;84:41-5.
274. Rashtak S, Khaleghi S, Pittelkow MR, Larson JJ, Lahr BD , Murray JA. Isotretinoin exposure and risk of inflammatory bowel disease. JAMA Dermatol 2014;150:1322-6.
275. 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.
276. 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 (Clinical research ed) 2010;341:c5812.
277. Chen YH, Wang WM, Chung CH, Tsao CH, Chien WC , Hung CT. Risk of psychiatric disorders in patients taking isotretinoin: A nationwide, population-based, cohort study in Taiwan. J Affect Disord 2022;296:277-82.
278. Paljarvi T, McPherson T, Luciano S, Herttua K , Fazel S. Isotretinoin and adverse neuropsychiatric outcomes: retrospective cohort study using routine data. Br J Dermatol 2022.
279. Ugonabo N, Love E, Wong PW, Rieder EA, Orlow SJ, Kim RH et al. Psychiatric disorders and suicidal behavior in patients with acne prescribed oral antibiotics versus isotretinoin: Analysis of a large commercial insurance claims database. J Am Acad Dermatol 2021;85:878-84.
280. Jick SS, Kremers HM , Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. Arch Dermatol 2000;136:1231-6.
281. Secrest AM, Hopkins ZH, Frost ZE, Taliercio VL, Edwards LD, Biber JE et al. Quality of Life Assessed Using Skindex-16 Scores Among Patients With Acne Receiving Isotretinoin Treatment. JAMA Dermatol 2020;156:1098-106.

282. Bray AP, Kravvas G, Skevington SM , Lovell CR. Is there an association between isotretinoin therapy and adverse mood changes? A prospective study in a cohort of acne patients. J Dermatolog Treat 2019;30:796-801.
283. Paljarvi T, McPherson T, Luciano S, Herttua K , Fazel S. Isotretinoin and adverse neuropsychiatric outcomes: retrospective cohort study using routine data. Br J Dermatol 2022;187:64-72.
284. Siu AL, Force USPST, Bibbins-Domingo K, Grossman DC, Baumann LC, Davidson KW et al. Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement. JAMA 2016;315:380-7.
285. Force USPST, Mangione CM, Barry MJ, Nicholson WK, Cabana M, Chelmow D et al. Screening for Depression and Suicide Risk in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. JAMA 2022;328:1534-42.
286. Force USPST, Mangione CM, Barry MJ, Nicholson WK, Cabana M, Coker TR et al. Screening for Anxiety in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. JAMA 2022;328:1438-44.
287. Schrom K, Nagy T , Mostow E. Depression screening using health questionnaires in patients receiving oral isotretinoin for acne vulgaris. J Am Acad Dermatol 2016;75:237-9.
288. Waldman A, Bolotin D, Arndt KA, Dover JS, Geronemus RG, Chapas A et al. ASDS Guidelines Task Force: Consensus Recommendations Regarding the Safety of Lasers, Dermabrasion, Chemical Peels, Energy Devices, and Skin Surgery During and After Isotretinoin Use. Dermatol Surg 2017;43:1249-62.
289. Strauss JS, Rapini RP, Shalita AR, Konecky E, Pochi PE, Comite H et al. Isotretinoin therapy for acne: results of a multicenter dose-response study. J Am Acad Dermatol 1984;10:490-6.
290. Tangjaturonrusamee C, Rattanaumpawan P , Ditre CM. Comparison of pneumatic broadband light plus adapalene gel 0.3% versus adapalene gel 0.3% monotherapy in the treatment of mild to moderate acne. Cutis 2016;98(1):56-61.
291. Scopelliti MG, Kothare A , Karavitis M. A novel 1726-nm laser system for safe and effective treatment of acne vulgaris. Lasers Med Sci 2022;37:3639-47.
292. Alexiades M, Kothare A, Goldberg D , Dover JS. Novel 1726 nm Laser Demonstrates Durable Therapeutic Outcomes and Tolerability for Moderate-to-Severe Acne Across Skin Types. J Am Acad Dermatol 2023.
293. Reynolds RC, Lee S, Choi JY, Atkinson FS, Stockmann KS, Petocz P et al. Effect of the glycemic index of carbohydrates on Acne vulgaris. Nutrients 2010;2:1060-72.
294. Kwon HH, Yoon JY, Hong JS, Jung JY, Park MS , Suh DH. Clinical and histological effect of a low glycaemic load diet in treatment of acne vulgaris in Korean patients: a randomized, controlled trial. Acta Derm Venereol 2012;92:241-6.
295. Smith RN, Mann NJ, Braue A, Makelainen H , Varigos GA. A low-glycemic-load diet improves symptoms in acne vulgaris patients: a randomized controlled trial. The American journal of clinical nutrition 2007;86:107-15.
296. Pavithra G, Upadya GM , Rukmini MS. A randomized controlled trial of topical benzoyl peroxide 2.5% gel with a low glycemic load diet versus topical benzoyl peroxide 2.5% gel with a normal diet in acne (grades 1-3). Indian J Dermatol Venereol Leprol 2019;85:486-90.
297. Barbieri JS, Tan JKL , Adamson AS. Active Comparator Trial Designs Used to Promote Development of Innovative New Medications. Cutis 2020;106:E4-E6.
298. Miller J, Ly S, Mostaghimi A , Barbieri JS. Use of Active Comparator Trials for Topical Medications in Dermatology. JAMA Dermatol 2021;157:597-9.
299. Gao Y, Wei EK, Arron ST, Linos E, Margolis DJ , Mansh MD. Acne, sexual orientation, and mental health among young adults in the United States: A population-based, cross-sectional study. J Am Acad Dermatol 2017;77:971-3.
300. Pathmarajah P, Peterknecht E, Cheung K, Elyoussfi S, Muralidharan V , Bewley A. Acne Vulgaris in Skin of Color: A Systematic Review of the Effectiveness and Tolerability of Current Treatments. J Clin Aesthet Dermatol 2022;15:43-68.

301. Braun H, Zhang Q, Getahun D, Silverberg MJ, Tangpricha V, Goodman M et al. Moderate-to-Severe Acne and Mental Health Symptoms in Transmasculine Persons Who Have Received Testosterone. JAMA Dermatol 2021;157:344-6.
302. DeGrazia TM, Rolader R, Thiboutot DM , Yeung H. Eligibility Criteria Related to Hormone Therapy in Acne Clinical Trials: A Systematic Review. J Invest Dermatol 2021;141:189-91.
303. . In: T. Becker, M. Chin and N. Bates editors. Measuring Sex, Gender Identity, and Sexual Orientation. Washington (DC)2022.
304. Yeung H, Luk KM, Chen SC, Ginsberg BA , Katz KA. Dermatologic care for lesbian, gay, bisexual, and transgender persons: Terminology, demographics, health disparities, and approaches to care. J Am Acad Dermatol 2019;80:581-9.
305. Butler DC, Heller MM , Murase JE. Safety of dermatologic medications in pregnancy and lactation: Part II. Lactation. J Am Acad Dermatol 2014;70:417 e1-10; quiz 27.
306. Harper JC, Baldwin H, Stein Gold L , Guenin E. Efficacy and Tolerability of a Novel Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate or Severe Acne Vulgaris in Adult Females. Journal of drugs in dermatology : JDD 2019;18(11):1147-54.
307. Lucky AW, Maloney JM, Roberts J, Taylor S, Jones T, Ling M et al. Dapsone gel 5% for the treatment of acne vulgaris: safety and efficacy of long-term (1 year) treatment. J Drugs Dermatol 2007;6:981-7.
308. Mazzetti A, Moro L, Gerloni M , Cartwright M. A Phase 2b, Randomized, Double-Blind Vehicle Controlled, Dose Escalation Study Evaluating Clascoterone 0.1%, 0.5%, and 1% Topical Cream in Subjects With Facial Acne. 2019;1:570.
309. Guerra-Tapia A. Effects of benzoyl peroxide 5% clindamycin combination gel versus adapalene 0.1% on quality of life in patients with mild to moderate acne vulgaris: a randomized single-blind study. J Drugs Dermatol 2012;11:714-22.
310. Langner A, Chu A, Goulden V , Ambroziak M. A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide and adapalene in the treatment of mild to moderate facial acne vulgaris. Br J Dermatol 2008;158:122-9.
311. Dogra S, Sumathy TK, Nayak C, Ravichandran G, Vaidya PP, Mehta S et al. Efficacy and safety comparison of combination of 0.04% tretinoin microspheres plus 1% clindamycin versus their monotherapy in patients with acne vulgaris: a phase 3, randomized, double-blind study. Journal of Dermatological Treatment 2021;32(8):925-33.
312. Tanghetti E, Dhawan S, Green L, Ling M, Downie J, Germain MA et al. Clinical evidence for the role of a topical anti-inflammatory agent in comedonal acne: findings from a randomized study of dapsone gel 5% in combination with tazarotene cream 0.1% in patients with acne vulgaris. J Drugs Dermatol 2011;10:783-92.
313. Kwon HH, Park SY, Yoon JY, Min S , Suh DH. Do tutorials on application method enhance adapalene-benzoyl peroxide combination gel tolerability in the treatment of acne? Journal of Dermatology 2015;42(11):1058-65.

Table I. Clinical Questions and Scope

Clinical Questions
CQ 1. What systems are most commonly used for the grading and classification of acne vulgaris in adults, adolescents, and preadolescents (≥ 9 years)?
CQ 2. What is the role of microbiological and endocrine testing in evaluating acne vulgaris in adults, adolescents, and preadolescents (≥ 9 years)s?
CQ 3. What are the effectiveness and safety of topical agents in the treatment of acne vulgaris in adults, adolescents, and preadolescents (≥ 9 years), including: • Retinoids (adapalene, tazarotene, tretinoin, and trifarotene) • Benzoyl peroxide • Topical antibiotics (erythromycin, clindamycin, dapsone, and minocycline) • Alpha hydroxy acid (glycolic acid) • Beta hydroxy acid (salicylic acid) • Azelaic acid • Topical antiandrogen (clascoterone) • Others (sulfur/sulfacetamide sodium and resorcinol) • Combinations of topical agents
CQ 4. What are the effectiveness and safety of systemic antibiotics in the treatment of acne vulgaris in adults, adolescents, and preadolescents (≥ 9 years), including: • Macrolides (azithromycin, clarithromycin, and erythromycin) • Penicillins (amoxicillin and ampicillin) • Cephalosporin (cephalexin) • Trimethoprim/sulfamethoxazole • Other (dapsone)
CQ 5.a. What are the effectiveness and safety of hormonal agents in the treatment of acne vulgaris in adults, adolescents, and preadolescents (≥ 9 years), including: • Combined contraceptive agents (estrogen and progestin) • Aldosterone receptor antagonist (spironolactone) • Oral corticosteroids (prednisolone and prednisone) • Intralesional corticosteroid (triamcinolone)
CQ 5.b. For patients on spironolactone, how often and for how long should potassium level be monitored?
CQ 6.a. What are the effectiveness and safety of isotretinoin in the treatment of acne vulgaris in adults, adolescents, and preadolescents (≥ 9 years)?
CQ 6.b. For patients on isotretinoin, how often and for how long should lipids, liver enzymes, creatine kinase, and blood count levels be monitored?
CQ 7. What are the effectiveness and safety of physical modalities for the treatment of acne vulgaris in adults, adolescents, and preadolescents (≥ 9 years), including: • Chemical peels (alpha hydroxy acid: glycolic acid, lactic acid, madelic acid; beta hydroxy acid: salicylic acid) • Comedo extraction • Lasers • Photodynamic/light therapy (blue light therapy, red light therapy, ALA, and IPL)
CQ 8. What are the effectiveness and safety of complementary/alternative therapies in the treatment of acne vulgaris in adults, adolescents, and preadolescents (≥ 9 years), including: • Botanicals/plant-derived agents (tea tree oil, green tea, and witch hazel) • Vitamin oral formulation (zinc, niacinamide, pantothenic acid) • Vitamin topical formulation (zinc and niacinamide)

CQ 9. What are the effectiveness and safety of diet in the treatment of acne vulgaris in adults, adolescents, and preadolescents (≥ 9 years), including:

- Low glycemic diet
- Low dairy diet
- Low whey diet
- Omega-3 and chocolate

ALA: aminolevulinic acid; IPL: intense pulsed light; US: United States

1676 **Table II. Strength of Recommendation and Certainty of Evidence**

Strength of Recommendation	**Wording**	**Implication[5-7]**
Strong recommendation *for* the use of an intervention	"We recommend…"	Benefits clearly outweigh risk and burdens; recommendation applies to most patients in most circumstances.
Strong recommendation *against* the use of an intervention	"We recommend against…"	Risk and burden clearly outweigh benefits; recommendation applies to most patients in most circumstances.
Good Practice Statement	"We recommend…"	Guidance was viewed by the Work Group as imperative to clinical practice and developed when the supporting evidence was considerable but indirect, and the certainty surrounding an intervention's impact was high with the benefits clearly outweighing the harms (or vice versa). Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high. Implementation of these strong recommendations is considered to clearly result in beneficial outcomes.[7]
Conditional recommendation *for* the use of an intervention	"We conditionally recommend…"	Benefits are closely balanced with risks and burden; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values.
Conditional recommendation *against* the use of an intervention	"We conditionally recommend against…"	Risks and burden closely balanced with benefits; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values
Certainty of Evidence	**Wording**	**Implication[5, 6]**
High	"high certainty evidence"	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	"moderate certainty evidence"	Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	"low certainty evidence"	Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very Low	"very low certainty evidence"	The estimate of effect is very uncertain; the true effect may be substantially different from the estimate of effect

1677

Table III. Recommendation for the management of acne vulgaris in adults, adolescents, and preadolescents (≥ 9 years)

No.	Recommendation	Strength	Certainty of Evidence	Evidence
Topical Agents				
1.1	When managing acne with topical medications, we recommend multimodal therapy combining multiple mechanisms of action.	Good Practice Statement		
1.2	For patients with acne, we recommend benzoyl peroxide.	Strong	Moderate	63, 64, 89-94
1.3	For patients with acne, we recommend topical retinoids.	Strong	Moderate	59, 60, 62-71, 73, 75-77, 306, 307
1.4	For patients with acne, we recommend topical antibiotics Remark: Topical antibiotic monotherapy is not recommended.	Strong	Moderate	65, 75, 90, 92, 93, 98-105, 107
1.5	For patients with acne, we conditionally recommend clascoterone.	Conditional[a]	High	121, 308
1.6	For patients with acne, we conditionally recommend salicylic acid.	Conditional	Low	122
1.7	For patients with acne, we conditionally recommend azelaic acid.	Conditional	Moderate	123, 124, 126
1.8	For patients with acne, we recommend fixed dose combination topical antibiotic with benzoyl peroxide	Strong	Moderate	90, 92, 93, 112, 115-119, 309, 310
1.9	For patients with acne, we recommend fixed dose combination topical retinoid with topical antibiotic. Remark: Concomitant use of benzoyl peroxide is recommended to prevent the development of antibiotic resistance.	Strong	Moderate	65, 75, 112, 311, 312
1.10	For patients with acne, we recommend fixed dose combination topical retinoid with benzoyl peroxide.	Strong	Moderate	63, 64, 110-114, 313
Systemic Antibiotics				
2.1	For patients with acne, we recommend doxycycline.	Strong	Moderate	132, 143-146
2.2	For patients with acne, we conditionally recommend minocycline.	Conditional	Moderate	132, 152-155
2.3	For patients with acne, we conditionally recommend sarecycline.	Conditional[a]	High	157-159
2.4	For patients with acne, we conditionally recommend doxycycline over azithromycin.	Conditional	Low	148-151
2.5	For patients with acne, we recommend limiting use of systemic antibiotics when possible to reduce the development of antibiotic resistance and other antibiotic associated complications.	Good Practice Statement		
2.6	It is recommended that systemic antibiotics are used concomitantly with benzoyl peroxide and other topical therapy.	Good Practice Statement		

Hormonal agents				
3.1	For patients with acne, we conditionally recommend combined oral contraceptive pills.	Conditional[b]	Moderate	167-176
3.2	For patients with acne, we conditionally recommend spironolactone. Remark: Potassium monitoring is not needed in healthy patients. However, consider potassium testing for those with risk factors for hyperkalemia (e.g., older age, medical comorbidities, medications).	Conditional	Moderate	209-216
3.3	For patients with larger acne papules or nodules, we recommend intralesional corticosteroid injections as an adjuvant therapy. Remark: Intralesional corticosteroid injections should be used judiciously for patients who are at risk of acne scarring and/or for rapid improvement in inflammation and pain. Using a lower concentration and volume of corticosteroid can minimize the risks of local corticosteroid adverse events.	Good Practice Statement		
Isotretinoin				
4.1	For patients with severe acne or for patients who have failed standard treatment with oral or topical therapy, we recommend isotretinoin. Remark: Acne patients with psychosocial burden or scarring should be considered as having severe acne and to be candidates for isotretinoin. For patients undergoing treatment with isotretinoin, monitoring of LFTs and lipids should be considered, but CBC monitoring is not needed in healthy patients. Population-based studies have not identified increased risk of neuropsychiatric conditions or inflammatory bowel disease in acne patients undergoing treatment with isotretinoin. For persons of childbearing potential, pregnancy prevention is mandatory.	Good Practice Statement		
4.2	For patients with severe acne, we conditionally recommend traditional daily dosing of isotretinoin over intermittent dosing of isotretinoin.	Conditional	Low	250, 251, 253
4.3	For patients prescribed isotretinoin, we conditionally recommend either standard isotretinoin or lidose-isotretinoin.	Conditional	High	241
Physical modalities				
5.1	For patients with acne, we conditionally recommend against adding pneumatic broadband light to adapalene 0.3% gel.	Conditional	Low	290

[a] Conditional recommendations were made for clascoterone and sarecycline due to high current cost of treatment that may impact equitable acne treatment access.

[b] Conditional recommendation was made for combined oral contraceptive pills due to the variability in patient values and preferences related to contraception and hormonal medications.

Table IV. Summary of contraindications to combined oral contraceptive use based on the US Medical Eligibility Criteria for Contraceptive Use.[1]

Absolute contraindications (Category 4: A condition that represents an unacceptable health risk if COC is used)	Relative contraindications (Category 3: A condition for which the theoretical or proven risks usually outweigh the benefits of COC)
Personal Characteristics and Reproductive History	
• Age ≥35 years and smoking ≥15 cigarettes daily • <21 days postpartum, regardless of breastfeeding status	• Age ≥35 years and smoking <15 cigarettes daily • Breastfeeding patient 21-29 days postpartum • Breastfeeding patient 30-42 days postpartum, with other VTE risk factors[2] • Non-breastfeeding patient 21-42 days postpartum, with other VTE risk factors[2]
Cardiovascular disease	
• SBP ≥160 mmHg or DBP ≥100 mmHg • Vascular disease • Acute VTE or history of VTE with ≥1 risk factor for recurrence[3] • Major surgery with prolonged immobilization • Known thrombogenic mutation[4] • Multiple risk factors for atherosclerosis[5] • Current or history of ischemic heart disease • Current or history of stroke • Valvular heart disease with complications[6] • Peripartum cardiomyopathy with normal or impaired cardiac function for <6 months or moderate or severely impaired cardiac function	• SBP 140-159 mmHg or DBP 90-99mmHg • Adequately controlled hypertension • VTE with no risk factors for recurrence • Superficial venous thrombosis • Peripartum cardiomyopathy with normal or mildly impaired cardiac function for ≥6 months
Gastrointestinal conditions	
• Acute or flare of viral hepatitis • Severe or decompensated cirrhosis • Hepatocellular adenoma • Malignant liver tumor (hepatoma)	• History of malabsorptive procedures (Roux-en-Y gastric bypass or biliopancreatic diversion) • Ulcerative colitis or Crohn disease with increased VTE risk[7] • Untreated or medically treated symptomatic gallbladder disease

	• History of COC-related cholestasis
• Diabetes with nephropathy, retinopathy, neuropathy, other vascular disease, or with duration > 20 years[8]	
• Current breast cancer • Migraine with aura • Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies • Solid organ transplantation complicated by acute or chronic graft failure, rejection, or cardiac allograft vasculopathy	• Past breast cancer with no evidence of disease for 5 years • Multiple sclerosis with prolonged immobility

BP, blood pressure; COC, combined oral contraceptives; VTE, venous thromboembolism

[1] Adapted from Curtis KM et al. Please refer to the US Medical Eligibility Criteria for Contraceptive Use 2016 for additional clarification, evidence, and comments related to important classification details on combined hormonal contraceptives.[187]

[2] Risk factors include age ≥35 years, previous VTE, thrombophilia, immobility, transfusion at delivery, peripartum cardiomyopathy, body mass index ≥30kg/m^2, postpartum hemorrhage, post-Cesarean delivery, preeclampsia, or smoking

[3] Risk factors include history of estrogen-related VTE, pregnancy-related VTE, idiopathic VTE, known thrombophilia (including antiphospholipid syndrome), active cancer (metastatic, receiving therapy, or within 6 months after clinical remission) excluding nonmelanoma skin cancer, or history of recurrent VTE

[4] Known thrombogenic mutations include factor V Leiden, prothrombin mutation, protein S deficiency, protein C deficiency, or anti-thrombin deficiency

[5] Risk factors include older age, smoking, diabetes mellitus, hypertension, low high-density lipoprotein, high low-density lipoprotein, or high triglycerides

[6] Complicated valvular heart disease include pulmonary hypertension, risk for atrial fibrillation, or history of subacute bacterial endocarditis

[7] Risk factors include active or extensive disease, surgery, immobilization, corticosteroid use, vitamin deficiencies, or fluid depletion

[8] Classification as absolute (class 4) or relative (class 3) contraindication is assessed based on severity of diabetes-related complications

Figure I. Management of acne vulgaris