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Review

A review of diagnosis and treatment of acne in adult female patients☆,☆☆

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ABSTRACT

This review focuses on the treatment options for adult female patients with acne. Acne in adult female patients may start during adolescence and persist or have an onset in adulthood. Acne has various psychosocial effects that impact patients' quality of life. Treatment of acne in adult women specifically has its challenges due to the considerations of patient preferences, pregnancy, and lactation. Treatments vary widely and treatment should be tailored specifically for each individual woman. We review conventional therapies with high levels of evidence, additional treatments with support from cohort studies and case reports, complementary and/or alternative therapies, and new agents under development for the treatment of patients with acne.

Introduction

Acne vulgaris (AV) is a disease of the pilosebaceous unit that causes noninflammatory lesions (open and closed comedones), inflammatory lesions (papules, pustules, and nodules), and varying degrees of scarring. AV is an extremely common condition with a lifetime prevalence of approximately 85% and occurs mostly during adolescence (Bhate and Williams, 2013). AV can persist into adulthood, with a 50.9% prevalence rate of acne in women ages 20 to 29 years versus 26.3% in women ages 40 to 49 years (Collier et al., 2008). Female patients account for two thirds of visits made to dermatologists for acne, and one third of all dermatology office visits for acne are by women who are older than 25 years (Yentzer et al., 2010).

Acne leads to significant morbidity that is associated with residual scarring and psychological disturbances such as poor self-image, depression, and anxiety, which leads to a negative impact on quality of life (Cunliffe, 1986; Ramos-e-Silva et al., 2015; Shuster et al., 1978). In one epidemiologic study by Yentzer et al. (2010), 8.8% of patients with acne reported depression with women suffering from depression twice as often as men (10.6% vs. 5.3%), but this was unrelated to acne severity.

Pathogenesis

Four key pathogenic processes lead to the formation of acne lesions: alteration of follicular keratinization that leads to comedones; increased and altered sebum production under androgen control; follicular colonization by *Propionibacterium acnes*; and complex inflammatory mechanisms that involve both innate and acquired immunity (Williams et al., 2012; Zaenglein et al., 2016). Genetics (twin studies Bataille et al., 2002, family history of severe acne Wei et al., 2010), diet (glycemic index Ismail et al., 2012; Kwon et al., 2012; Smith et al., 2007a, 2007b, 2008), including chocolate (Grant and Anderson, 1965; Magin et al., 2005) and dairy consumption (Adebamowo et al., 2006, 2008; Di Landro et al., 2012); and environmental factors (smoking Klaz et al., 2006; Schafer et al., 2001, occlusive cosmetics Plewig et al., 1970, occupational exposures Tucker, 1983) also contribute to the pathogenesis of acne.

The pathogenesis of acne in adult women is particularly complex. Androgens play a major role (Harper, 2008; Lucky et al., 1994, 1997), as evidenced by the response of acne in adult women to hormonal treatments, especially in the context of hyperandrogenism disorders such as polycystic ovary syndrome (PCOS) and the use of hormone-based therapies such as oral contraceptive and anti-

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androgen medications in women with normal androgen levels (Lolis et al., 2009). In addition, the lack of acne in androgen-insensitive women (Imperato-McGinley et al., 1993; Thiboutot, 2004) and rising levels of dehydroepiandrosterone sulfate in association with the onset of acne in premenarchal girls and a subset of patients with PCOS also play a major role (Lucky et al., 1994; Chen et al., 2011). Androgens stimulate sebum production via androgen receptors on the sebaceous glands.

Clinical presentation

Acne in women can occur at any age and with varying degrees of severity. Female patients may more frequently develop lesions on the lower third of the face, especially on the chin and jawline (Kamangar and Shinkai, 2012). However, a more recent epidemiologic study by Dreno et al. (2015) suggests that this hormonal distribution may not be the most common clinical presentation of acne in adult women.

Acne lesions range from comedones (Fig. 1) to papules and pustules (Fig. 2), cysts, and/or nodules (Fig. 3). In one study of postadolescent acne, 85% of patients had mostly comedonal acne (Capitanio et al., 2010) with two subtypes identified as persistent and late-onset acne (Ramos-e-Silva et al., 2015). Persistent acne, which is defined as acne that persists beyond adolescence into adulthood, accounts for 80% of cases in adult female patients (Holzmann and Shakery, 2014). Late-onset acne is defined as acne that begins after the age of 25 years (Holzmann and Shakery, 2014; Ramos-e-Silva et al., 2015). Women with signs of hyperandrogenism such as hirsutism or menstrual irregularities and those with true late-onset acne should be further evaluated for an underlying endocrine disorder such as PCOS.

To date, there is no universally agreed-upon grading system for acne, and the grading systems used in clinical trials vary greatly (Zaenglein et al., 2016). Acne grading systems should take into account the type and severity of the acne, number of lesions, anatomic location and the extent of the acne, patient quality of life and other psychosocial metrics, and scarring (Zaenglein et al., 2016). Tan et al. (2013) evaluated 18 global acne grading scales with grading methods that ranged from text descriptions, grades for number and type of lesions, grades for severity, grades for comedonal versus inflammatory acne to the use of standardizing photographs.

Two groups of grading scales exist including those that use quantitative measures such as lesion counts and numeric ranges and those that are based on qualitative descriptions. Quantitative scales include those that specify the number and type of primary acne lesions (Del Rosso et al., 2007; Hayashi et al., 2008; Plewig and Kligman, 1975) and those that assign weights to lesion types to generate a severity index (Doshi et al., 1997; Liden et al., 1980; Michaelsson et al., 1977). Qualitative scales use adjectives such as few, some, and numerous to quantify lesions. There are also scales that solely use photographic templates of varying severity (Burke and Cunliffe, 1984; O'Brien et al., 1998).

Evaluation considerations

The evaluation of any patient with acne should include a thorough medical history and physical examination. Medications and supplement use, social history including tobacco and illicit drug use, menstrual history (i.e., age of menarche, regularity of menses, history of infertility), and prior/current acne treatments must be elucidated (Kamangar and Shinkai, 2012). A complete review of systems should be conducted to seek symptoms of hyperandrogenism or other endocrinology disorders.

Signs and symptoms of hyperandrogenism include acne, hirsutism, seborrhea, androgenetic alopecia, amenorrhea, oligomenorrhea, virilization, clitoromegaly, infertility, polycystic ovaries, increased muscle mass, and decreased breast size (Harper, 2008; Lolis et al., 2009). Of these, hirsutism is the most common manifestation of hyperandrogenism and 70% of women with hirsutism have hyperandrogenism (Lucky, 1995). Hirsutism is highly associated with elevated serum levels of free testosterone. Given that hair removal may obscure a clinician recognition of hirsutism, patients should be asked about the nature and frequency of hair removal practices as well as the locations of hair overgrowth. If patients exhibit signs or symptoms of hyperandrogenism, a thorough endocrinologic work-up should be initiated.

The differential diagnosis of acne in adult female patients is detailed in Table 1, along with distinguishing characteristics. In addition, underlying systemic causes for acne including hyperandrogenism should be assessed. Causes of drug-induced acne are detailed in Table 2.

Further testing

Microbiologic testing

P. acnes is thought to be an important pathogen in the development of acne. Routine cultures are not done unless gram-negative folliculitis or *Staphylococcus aureus* folliculitis are considered in the differential diagnosis (Zaenglein et al., 2016).

Gram-negative folliculitis presents as monomorphic eruptive pustules in the perioral, beard, and neck distribution and typically in the setting of prolonged oral tetracycline use (Zaenglein et al., 2016). Gram-negative folliculitis is caused by gram-negative microbes such as *Klebsiella* and *Serratia* and is treated with isotretinoin. Microbe-directed therapy may be considered given the clinical setting and individual patient characteristics. The American Academy of Dermatology (AAD) 2016 working group on the management of acne vulgaris only recommends microbiologic testing for those who exhibit acne-like lesions that are suggestive of gram-negative folliculitis and not otherwise (Zaenglein et al., 2016).

Endocrine testing

The role of androgens in acne is well established. Endocrine testing is only needed in patients who have other signs or symptoms of hyperandrogenism. The most common cause of increased androgens in adult women is PCOS (Lucky, 1983). Clinically, hyperandrogenism

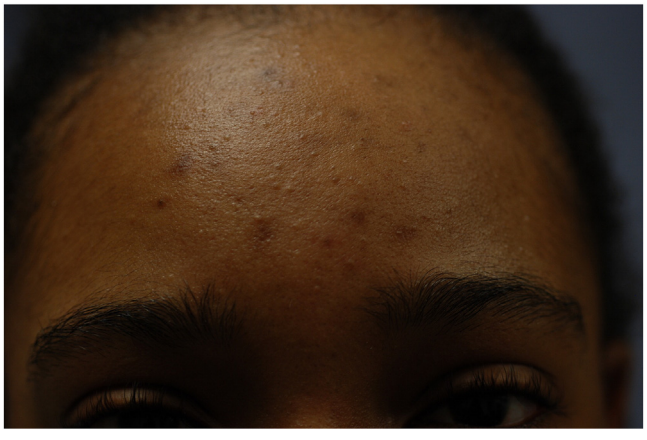

Figure 1. Comedones with post-inflammatory hyperpigmentation. Courtesy of Bethanee Schlosser, MD, PhD.

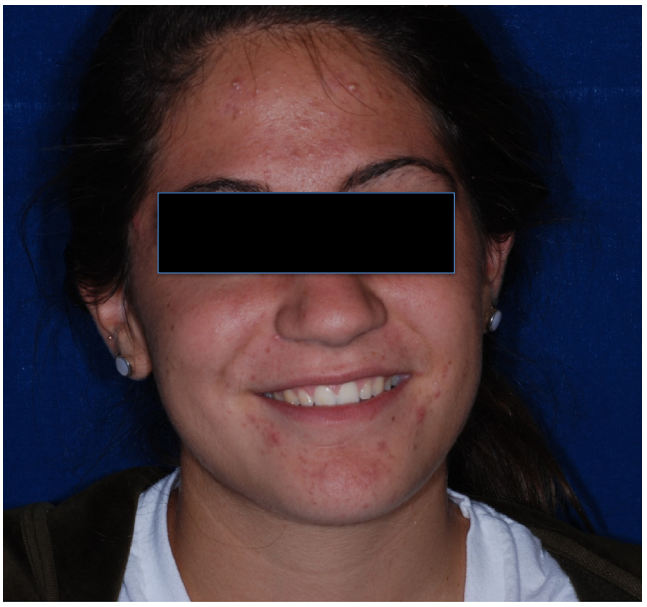

Figure 2. Inflammatory papules and pustules.
Courtesy of Bethanee Schlosser, MD, PhD.

can manifest by unwanted hair growth/hirsutism, seborrhea, acne, and/or androgenetic alopecia (Azziz et al., 2009). Significant virilization suggests disorders of severe insulin resistance, androgen-secreting tumors, and androgenic substance abuse (Azziz et al., 2009). A laboratory test panel to screen for PCOS includes free and total testosterone, dehydroepiandrosterone sulfate, androstenedione, luteinizing hormone, and follicle-stimulating hormone (Azziz et al., 2009; Lawrence et al., 1981; Lucky, 1983; Lucky et al., 1983, 1997; Seirafi et al., 2007; Timpatanapong and Rojanasakul, 1997). The differential diagnosis of PCOS includes thyroid disease, prolactin excess, nonclassical congenital adrenal hyperplasia, and other rare endocrinology disorders (Zaenglein et al., 2016).

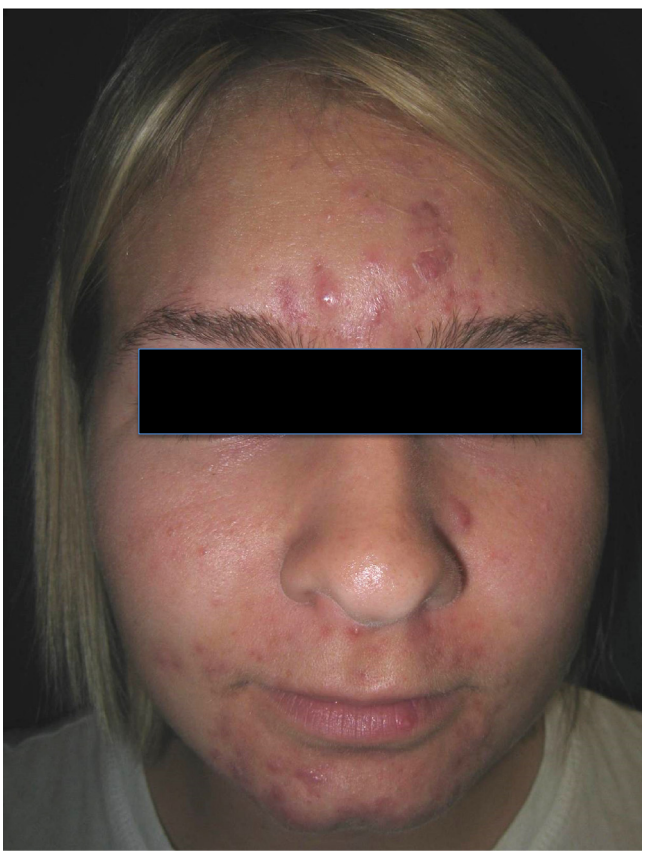

Figure 3. Acne Nodules and Cysts.
Courtesy of Bethanee Schlosser, MD, PhD.

Women who are already prescribed oral contraceptive medications and display additional signs of androgen excess should have similar testing done, although oral contraceptive pills may be beneficial to women with clinical and laboratory findings of hyperandrogenism as well as in women without these findings (Zaenglein et al., 2016). An endocrinologist should evaluate patients with abnormal hormone levels. The AAD working group only recommends laboratory evaluations for patients who have acne and additional signs of androgen excess (Zaenglein et al., 2016).

Treatment of acne vulgaris

Table 3 shows the various treatments for patients with AV, along with the strength of recommendations from the AAD working group but modified to include pregnancy and lactation ratings. This review article focuses on topical therapies, systemic antibiotic medications, isotretinoin, and novel therapies under development. We emphasize limiting treatment duration of systemic antibiotic medications in adults with acne and prescribing concomitant and/or maintenance treatment with topical therapy. A more complete discussion on the use of hormonal agents can be found in an article by Trivedi et al. (2017) entitled "A review of hormone-based therapies for adult acne vulgaris in women," which was also published in the *International Journal of Women's Dermatology*. Table 4 shows the AAD working group's treatment algorithm for the management of AV in adolescents and young adults, which requires an adjustment on the basis of patient risk factors, types and sites of acne lesions, and age.

The treatment of acne is challenging and often chronic, with high rates of failure and numerous choices. A good therapeutic relationship with the patient is important to establish as well as setting realistic treatment goals. Frequent evaluations (i.e., every 8-12 weeks) are important to enable appropriate monitoring, manage adverse effects, and evaluate for medication compliance (Kamangar and Shinkai, 2012). Patient counseling is critical, especially to establish a time course for medication efficacy and discuss future therapeutic modalities in case of treatment failure or intolerability.

Treatment of acne vulgaris in adult women

The central tenets of acne management as displayed in Table 4 should be followed in the treatment of adult female patients. However, additional considerations exist that should be kept in mind during treatment. Women over the age of 25 years tend to have high rates of treatment failure (Kamangar and Shinkai, 2012). Approximately 80% of women fail multiple courses of systemic antibiotic medications and approximately 30% to 40% fail after a course of isotretinoin (Blasiak et al., 2013; Goulden et al., 1997a, b; Rademaker, 2016). Suspicion of an underlying endocrinology disorder should be heightened if a recurrence of acne appears shortly after treatment with isotretinoin (Lowenstein, 2006).

Treatment of acne vulgaris during pregnancy and lactation

Women of childbearing potential should also be asked about their plans for reproduction, and treatment should be tailored for safety, whether the patients are actively trying to conceive, pregnant, or

Table 1
Differential diagnosis of acne vulgaris

Disease/condition	Differentiating characteristics
Acne keloidalis nuchae	Often seen in black patients; lesions localized to the posterior neck; initially papules and pustules that may progress to confluent keloids
Acneiform eruptions	Secondary to systemic medications, topical corticosteroid medications, contrast dye, and cosmetic products; may be abrupt in onset and correlation with exposure; improvement with cessation of exposure (See Table 2 for agents that cause drug-induced acne)
Chloracne	Comedones, pustules, and cysts that localize to the post-auricular area, axillae, and groin; history of exposure to halogenated aromatic hydrocarbons; patient may have other systemic manifestations
Favre-Racouchot	Open and closed comedones on periorbital and malar areas; no inflammatory lesions; patients are usually older with a history of significant sun exposure
Bacterial folliculitis (non-gram-negative)	Erythematous papules and pustules that are follicularly-based; often affects trunk and extremities
Gram-negative folliculitis	Frequently occurs in patients with acne who have been on long-term antibiotic medications; pustules and nodules; may also occur in HIV+ patients, and after hot tub exposure; lesions may be cultured if acneiform lesions do not respond to typical antibiotic regimen
Lupus miliaris disseminatus faciei	Yellow/brown/red smooth papules in the periorbital and eyelid skin; biopsy shows caseating epithelioid granulomas
Milia	White keratinaceous cysts; lesions are usually persistent; noninflammatory
Periorificial dermatitis	Papules and pustules in the periorificial distribution; often exacerbated by topical corticosteroid use
Pyoderma faciale	Rapid onset of erythema, abscesses, cysts, and possible sinus tracts, no comedones
Rosacea	Various forms; background erythema with inflammatory papules and pustules often superimposed; environmental factors often can trigger
Syringoma	Noninflammatory papules that typically localize to the eyelids and malar cheeks; skin biopsy test results show dilated cysts with tadpole appearance
Adenoma sebaceum	Small waxy papules over the medial cheeks, nose, and forehead; multiple lesions associated with tuberous sclerosis; skin biopsy test results show dermal fibrosis and vascular proliferation and dilatation (angiofibromas). Facial angiofibromas are also a feature of multiple endocrine neoplasia type I and, rarely, Birt-Hogg-Dubé syndrome.

Hughes et al., 1983; Parsad et al., 2001.

Table 2
Causative agents of drug-induced acneiform eruptions

Class of agent	Examples
Hormones	
	Corticosteroids and corticotropin
	Androgens and anabolic Steroid medications
	Hormonal contraceptive medications
Neuropsychotherapeutic drugs	
	Tricyclic antidepressant medications
	Lithium
	Antiepileptic drugs
	Aripiprazole
	Selective serotonin reuptake inhibitors
Vitamins	
	Vitamins B1, B6, and B12
Cytostatic drugs	
	Dactinomycin (actinomycin D)
Immunomodulating molecules	
	Cyclosporine
	Sirolimus
Antituberculosis drugs	
	Isoniazid
	Rifampin
	Ethionamide
Halogens	
	Iodine
	Bromine
	Chlorine
Targeted therapies	
	Epidermal growth factor receptor inhibitors
	Multitargeted tyrosine kinase inhibitors
	Vascular endothelial growth factor inhibitor
	Proteasome inhibitor
	Tumor necrosis factor alfa inhibitors
	Histone deacetylase inhibitor

Kim and Kim, 2012.

lactating (Table 3). Among the physiologic changes of pregnancy is a rise in serum androgen levels (Bozzo et al., 2011), which results in increased sebaceous gland activity and often worsening of the acne. Published information on the effects of acne medications on the developing fetus or breastfeeding infant is very limited (Kong and Tey, 2013). Pregnancy and lactation are often part of the exclusion criteria in clinical trials; therefore, available information on medication-related teratogenicity and effects on lactation are often derived from case reports and animal studies.

The most widely used pregnancy classification is the U.S. Food and Drug Administration (FDA) assessment system, which stratifies drugs into five risk categories (Table 5). However, this classification system has been criticized for its large focus on animal data and frequent classification of new medications as class B (safe in pregnancy; Kong and Tey, 2013) as well as its excessive simplicity and lack of information about the severity and nature of possible side effects on the fetus (Public Affairs Committee of the Teratology Society, 2007). More recently, the FDA released the Pregnancy and Lactation Labeling Rule, which went into effect on June 30, 2015. The most significant change is the abolishment of pregnancy labeling categories for pharmaceuticals (A, B, C, D, and X), which was replaced with individualized narrative summaries for each medication that include "risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation" (Danesh and Murase, 2015).

The most commonly used risk classification systems for lactation are from the American Academy of Pediatrics (AAP), Hale (2010), and the recent Drug and Lactation Database (LactMed) that was produced by the National Library of Medicine. For the purposes of this review, the AAP and LactMed rating systems will be discussed.

The AAP system stratifies drugs into three categories: those that should be used with concern; those with unknown effects but may be of concern; and those that are generally compatible with breastfeeding (American Academy of Pediatrics Committee on Drugs, 2001). The LactMed system is a peer-reviewed database that provides comprehensive information about drugs that may be used in mothers who breastfeed including serum drug levels, adverse effects on infants, and alternative drugs to consider (U.S. National Library of Medicine, 2017).

Given the lack of data, a lack of unified drug classifications for women who are pregnant or lactating, and the serious risk of teratogenicity, clinicians tend to take a conservative approach to treating acne in this group of women. Additionally, primary practitioners and dermatologists have a popular view that acne is a cosmetic issue, which further leads clinicians to choose less effective treatments or even withhold treatment during pregnancy and lactation (Kong and Tey, 2013).

Topical therapies

Topical therapies are considered one of the mainstay treatments for patients with mild-to-moderate acne (Nast et al., 2012). These topical

Table 3
AAD 2016 Working Group strength of recommendations for the management and treatment of patients with acne vulgaris[a]

Recommendation	Strength of recommendation[b]	Level of evidence[c]	FDA classification system pregnancy rating[d]	Lactation rating	
				AAP classification system	LactMed[d]
Topical therapies					
Benzoyl peroxide	A	I, II	C	Not rated	Low risk
Topical antibiotic medications (e.g., clindamycin and erythromycin)	A	I, II	B	Compatible	Acceptable
Combination of topical antibiotic medications and benzoyl peroxide	A	I			
Topical retinoid medications (e.g., tretinoin, adapalene, and tazarotene)	A	I, II	Tretinoin – C Adapalene - C Tazarotene - X	Not rated	Low risk
Combination of topical retinoid medications and benzoyl peroxide/topical antibiotic medication	A	I, II			
Azelaic acid	A	I	B	Not rated	Low risk
Dapsone	A	I, II	C	Compatible	Avoid in G6PD deficiency, newborn/premature infants
Salicylic acid	B	II	C	Not rated	Not rated
Systemic antibiotic medications					
Tetracyclines (e.g., tetracycline, doxycycline, and minocycline)	A	I, II	D	Compatible	Short-term use acceptable
Macrolides (e.g., azithromycin and erythromycin)	A	I	B	Compatible	Acceptable
Trimethoprim (with or without sulfamethoxazole)	B	II	C	Compatible	Avoid in jaundiced, ill, premature infants
Limiting treatment duration and concomitant/maintenance topical therapy	**A**	**I, II**			
Hormonal agents					
Combined oral contraceptive medications	A	I	X	Compatible	Avoid <4 weeks post-partum
Spironolactone	B	II, III	C	Compatible	Appears acceptable
Flutamide	C	III	D	Not rated	Not rated
Oral corticosteroid medications	B	II	C	Compatible	Acceptable
Isotretinoin					
Conventional dosing	A	I, II	X	Not rated	No recommendation made
Low-dose treatment for moderate acne	A	I, II	X	Not rated	No recommendation made
Monitoring	B	II			
iPledge enrollment and contraception use	A	II			
Novel therapies					
Minocycline foam					
Topical nitric oxide-releasing agent					
Cortexolone 17α-propionate					

AAD, American Academy of Dermatology; AAP, American Academy of Pediatrics; FDA, U.S. Food and Drug Administration; LactMed, Drug and Lactation Database.

[a] Modified from Zaenglein et al., 2016, Table 3, to include pregnancy and lactation ratings (Lowenstein, 2006).

[b] Clinical recommendations from the AAD were developed on the best available evidence tabled in the guideline. The strength of the recommendation was ranked as follows: A. Recommendation based on consistent and good-quality patient-oriented evidence; B. Recommendation based on inconsistent or limited-quality patient-oriented evidence; C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

[c] Evidence was graded using a three-point scale on the basis of the quality of methodology and overall focus of the study as follows: I. Good-quality, patient-oriented evidence; II. Limited-quality, patient-oriented evidence; III. Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence.

[d] Produced by the U.S. National Library of Medicine.

agents are available over the counter and by prescription. More recently, several topical therapy combinations have been developed to treat patients with acne. The absorption of topical therapies is influenced by many factors, including the amount of agent applied, surface area of the application, length of the application time, frequency of the application, application to broken skin/erosions, choice of vehicle used, and thickness of the stratum corneum (Meredith and Ormerod, 2013).

Generally, topical agents are considered safer than oral medications for use in women who are pregnant or lactating because systemic availability of the drug is lower. Some topical medications do not even have a pregnancy category because systemic absorption is generally considered minimal unless use is extensive, intensive, or prolonged (Meredith and Ormerod, 2013).

Commonly used topical treatments for patients with acne include benzoyl peroxide (BP), salicylic acid (SA), antibiotic medications, combination antibiotic medications with BP, retinoid medications, retinoid with BP, retinoid with antibiotic medication, azelaic acid, and sulfone agents (Zaenglein et al., 2016).

Benzoyl peroxide

BP is commonly used to treat patients with acne and is available in a variety of strengths (2.5-10%) and formulations (cream, gel, wash, foam, aqueous gel, leave-on, and wash-off). BP is a comedolytic, keratolytic, anti-inflammatory agent with antimicrobial properties. BP is bactericidal mainly against *P. acnes* by the production of reactive oxygen radicals and has not developed resistance (Tanghetti, 2008). The addition of BP to antibiotic therapy enhances results and may reduce antibiotic resistance development (Zaenglein et al., 2016). Topical BP in varying formulations may be used 1 to 3 times daily as tolerated.

The use of BP is limited by concentration-dependent irritation, staining and bleaching of fabric, and uncommon contact allergy (Zaenglein et al., 2016). Lower concentrations (2.5-5%), water-based, and wash-off agents may be better tolerated in patients with more sensitive skin (Mills et al., 1986; Zaenglein et al., 2016).

Some clinicians are reluctant to prescribe BP concurrently with topical tretinoin due to the belief that BP may cause oxidation and

Table 4
American Academy of Dermatology 2016 Working Group treatment algorithm for the management of adolescents and young adults with acne vulgaris[a]

	Mild	Moderate	Severe
First-line Treatment	BP or topical retinoid -or- Topical combination therapy[b] (BP + antibiotic or retinoid + BP or retinoid + BP + antibiotic)	Topical combination therapy[b] (BP + antibiotic or retinoid + BP or retinoid + BP + antibiotic) -or- Oral antibiotic + topical retinoid + BP -or- Oral antibiotic + topical retinoid + BP + topical antibiotic	Oral antibiotic + topical combination therapy[b] (BP + antibiotic or retinoid + BP or retinoid + BP + antibiotic) -or- Oral isotretinoin
Alternative treatment	Add topical retinoid or BP (if not on already) -or- Consider alternate retinoid -or- Consider topical dapsone	Consider alternate combination therapy -or- Consider change in oral antibiotic -or- Add combined oral contraceptive or oral spironolactone (females) -or- Consider oral isotretinoin	Consider change in oral antibiotic -or- Add combined oral contraceptive or oral spironolactone (females) -or- Consider oral isotretinoin

BP, benzoyl peroxide.
[a] Modified from Zaenglein et al., 2016, Figure 1.
[b] Drug may be prescribed as a fixed combination product or as separate component.

degradation of the tretinoin molecule and thereby reduce its effectiveness. However, BP-induced degradation of tretinoin does not apply to all topical tretinoin formulations and multiple studies show the stability of tretinoin concentration and safety when using micronized tretinoin gel (0.05%) in combination with BP (Del Rosso et al., 2010; Gupta et al., 2015; Pariser et al., 2010; Torok and Pillai, 2011).

Table 5
Summary of U.S. Food and Drug Administration categories for medication use in pregnancy

Category	Description
A	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy.
B	No evidence of risk in humans. Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities despite adverse findings in animals. -or- In the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote but remains a possibility
C	Risk cannot be ruled out. Adequate, well-controlled human studies are lacking and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy but the potential benefits may outweigh the potential risk
D	Positive evidence of risk. Studies in humans or investigational or post-marketing data have demonstrated fetal risk. Nevertheless, potential benefits from the use of the drug may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
X	Contraindicated in pregnancy. Studies in animals or humans or investigational or post-marketing reports have demonstrated positive evidence of fetal abnormalities or a risk that clearly outweighs any possible benefit to the patient
N	No pregnancy category has been assigned

Salicylic acid

SA is a comedolytic agent that is available over the counter in 0.5 to 2% strengths and in both wash-off and leave-on preparations. SA is generally well tolerated by patients, but its efficacy in acne is limited (Shalita, 1981, 1989). BP and SA are the most widely used over-the-counter, topical, acne treatments and are often used in combination. SA may be applied 1 to 3 times daily as tolerated. SA has an FDA pregnancy rating of C.

Topical antibiotic medications

Topical antibiotic medications are thought to accumulate in the follicle and may work through both anti-inflammatory and antibacterial effects (Mills et al., 2002). Due to increasing antibiotic resistance, monotherapy with topical antibiotic medications in the management of acne is not recommended. Topical antibiotic medications are best used in combination with BP (Zaenglein et al., 2016). The main topical antibiotic medications are clindamycin and erythromycin.

Topical clindamycin

Clindamycin is available in a gel, lotion, pledget, or topical solution and has been assigned FDA pregnancy category B. The clindamycin 1% solution or gel is currently the preferred topical antibiotic medication (Padilla et al., 1981). The recommended dosing is an application of a thin layer once daily.

Topical erythromycin

Erythromycin is available as a gel, solution, ointment, pledget, or thin film. Oral and topical erythromycin formulations are both classified as FDA category B. Topical erythromycin is less efficacious in patients with acne than clindamycin because of *P. acnes* resistance

(Becker et al., 1981; Kuhlman and Callen, 1986; Leyden et al., 1987; Mills et al., 2002; Shahlita et al., 1984). Stable, fixed-combination agents are available with erythromycin 3% plus BP 5%, clindamycin 1% plus BP 5%, and clindamycin 1% plus BP 3.75% (Lookingbill et al., 1997; Pariser et al., 2014; Tschen et al., 2001). Combination agents may enhance compliance with treatment regimens (Zaenglein et al., 2016). Topical erythromycin is usually administered 1 to 2 times daily.

Topical retinoid medications

Topical retinoid medications are vitamin A–derivative prescription agents (Bradford and Montes, 1974; Krishnan, 1976; Lucky et al., 1998; Shalita et al., 1999). Topical retinoid medications are often used as first-line treatment for patients with mild-to-moderate acne, especially when the acne is mainly comedonal. Retinoid therapy is comedolytic and resolves the precursor microcomedone lesion. Retinoid medications are also anti-inflammatory and work in combination with other topical agents for all acne variants (Zaenglein et al., 2016). Topical retinoid treatments are the mainstay in the maintenance of clearance after discontinuation of oral therapy (Zaenglein et al., 2016). The recommended dosing is application of a thin layer once daily.

Three topical retinoid medications are used in the treatment of patients with acne: tretinoin (0.025-0.1% in cream, gel, or microsphere gel vehicles), adapalene (0.1% cream, gel, or lotion and 0.3% gel), and tazarotene (0.05%, 0.1% cream, gel, or foam). Retinoid use is limited by side effects including dryness, peeling, erythema, and irritation, which can be mitigated by reducing the volume used, the frequency of the application, and/or concomitant use of emollients (Pedace and Stoughton, 1971). Generally, therapy is initiated best every other day and then increased to daily as tolerated. The proper amount to use (e.g., pea size) is also important, as is ensuring even distribution with a thin layer and avoiding sensitive areas (e.g., eyelids, perioral area, nasal creases, and mucous membranes). With any of the topical retinoid treatments, higher concentrations are more efficacious but have greater side effects (Christiansen et al., 1974; Cunliffe et al., 1997; Krishnan, 1976). Additionally, topical retinoid medications increase the risk of photosensitivity so sunscreen lotion should be used concurrently.

Generic formulations of tretinoin are typically not photostable and should be applied in the evening. Coadministration of BP with tretinoin also leads to oxidation and inactivation of tretinoin; therefore, these agents should be applied at different times (i.e., BP in the morning, tretinoin at night). The micronized tretinoin formation as well as adapalene and tazarotene do not have similar restrictions.

Available combination agents that contain retinoid include adapalene 0.1% plus BP 2.5% and adapalene 0.3% plus BP 2.5% gels, which are approved for use in patients older than 9 years. In addition, clindamycin phosphate 1.2% plus tretinoin 0.025% gel is approved for patients older than 12 years of age (Dreno et al., 2014; Zouboulis et al., 2000).

There are conflicting reports on the safety of topical retinoid medications in women who are pregnant or lactating. Isolated cases have been reported of congenital malformations that were temporally associated with the use of these agents (Autret et al., 1997; Lipson et al., 1993; Loureiro et al., 2005; Navarre-Belhassen et al., 1998; Panchaud et al., 2012; Selcen et al., 2000). However, a large observational prospective study of 235 women who were exposed to a topical retinoid during their first trimester were compared with 444 women in the control group and no statistically significant differences in the rates of spontaneous abortions and minor or major birth defects were detected (Panchaud et al., 2012). A formal consensus on the safety of topical retinoid medications during pregnancy is lacking (van Hoogdalem, 1998). Additionally, manufacturers advise that these agents should not be used during pregnancy. Tretinoin and adapalene are classified as FDA pregnancy category C but tazarotene is category X. Patients should be counseled on these pregnancy risks when initiating retinoid treatment if they desire pregnancy.

Azelaic acid

Azelaic acid acts as a comedolytic, antimicrobial, and anti-inflammatory agent (Strauss et al., 2007) and is a naturally occurring dicarboxylic acid that is found in whole-grain cereals such as wheat, rye, and barley (Frampton and Wagstaff, 2004). Azelaic acid should be used with caution in patients with sensitive skin due to side effects that include redness, burning, and irritation.

Azelaic acid should also be used with caution in patients with Fitzpatrick skin types IV or greater because of its potential lightening effect (Cunliffe and Holland, 1989; Katsambas et al., 1989; Kircik, 2011). However, because of this side effect, azelaic acid is a useful adjunctive in acne treatment because it aids in the treatment of postinflammatory dyspigmentation.

The dosing recommendation is application of a thin film to the affected areas twice daily. Azelaic acid is categorized as FDA pregnancy class B because animal studies have shown no teratogenicity, but data on humans are not available.

Dapsone

Dapsone is a sulfone agent that is available in a 5% gel and used as a twice-daily agent or 7.5% gel used once daily. Data only show modest-to-moderate efficacy in the reduction of inflammatory acne lesions (Draelos et al., 2007; Lucky et al., 2007). Dapsone has a poorly understood mechanism in the treatment of patients with acne and its ability to kill *P. acnes* has been studied poorly (Zaenglein et al., 2016). Similar to other topical antibiotic treatments, dapsone is thought to work as an anti-inflammatory agent. The recommended dosing is application of a thin layer twice daily.

Dapsone should be used cautiously in combination with BP because coapplication may cause reversible, orange-brown discoloration of the skin, which can be brushed or washed off. Systemic absorption of topical dapsone is thought to be minimal so baseline glucose-6-phosphate dehydrogenase testing is not required. Topical dapsone is classified as FDA pregnancy category C.

Other topical agents

The following topical agents lack evidence-based data for their use in patients with acne but have been demonstrated to be effective in clinical practice: sodium sulfacetamide (Lebrun, 2004; Tarimci et al., 1997; Thiboutot, 2000), sulfur (Elstein, 1981), resorcinol (Elstein, 1981), aluminum chloride (Hjorth et al., 1985; Hurley and Shelley, 1978), topical zinc (Bojar et al., 1994; Cochran et al., 1985), and niacinamide (Khodaeiani et al., 2013; Shalita et al., 1995).

Systemic antibiotic medications

Oral antibiotic medications are commonly prescribed as second-line therapy for patients with mild-to-moderate acne that is not adequately controlled with topical agents alone and are a mainstay of acne treatment in patients with moderate-to-severe inflammatory acne. Oral antibiotic agents should be used in combination with a topical retinoid and BP if tolerated (Gold et al., 2010; Tan et al., 2014; (Zaenglein et al., 2013).

Given the rise in antibiotic resistance, monotherapy with oral antibiotic medications is strongly discouraged (Moon et al., 2012; Zaenglein et al., 2016). The Centers for Disease Control and Prevention has stressed antibiotic stewardship and limit antibiotic use to the shortest possible duration, ideally 3-4 months (Zaenglein et al., 2016), to reduce the risk of resistance. Concurrent and continued

use with a retinoid or retinoid/BP combination can assist in weaning off the systemic antibiotic (Gold et al., 2010; Leyden et al., 2006; Poulin et al., 2011; Tan et al., 2012; Thiboutot et al., 2006).

Limiting systemic antibiotic use may also reduce the risk of inflammatory bowel disease (for tetracyclines; Margolis et al., 2010), pharyngitis (for tetracyclines; Margolis et al., 2012), *C. difficile* infection (Bartlett et al., 1978; Carroll and Bartlett, 2011), and candida vulvovaginitis; however, studies have shown that these associations are limited. Penicillin, erythromycin, and cephalosporin are thought to have the best safety profile during pregnancy (Hernandez-Diaz et al., 2000).

Of note, there is limited evidence on the administration of antibiotic agents and the potential impact on the effectiveness of oral contraceptive pills (Hoffmann et al., 2015). Although a large epidemiological study that was conducted in the United States showed that there is no association between concomitant antibiotic use and the risk of breakthrough pregnancy among oral contraceptive pill users (Guengerich, 1990), other studies have shown a potential relationship (Back et al., 1980; Bainton, 1986; Fazio, 1991; Skolnick et al., 1976). There are three categories of antibiotic agents that range from those that are likely to reduce the effectiveness of OCPs (rifampin), those that are associated with OCP failure in three or more reported cases (ampicillin, amoxicillin, metronidazole, and tetracycline), and those that were associated with OCP failure in at least one case report (cephalexin, clindamycin, dapsone, erythromycin, griseofulvin, isoniazid, phenoxymethylpenicillin, talampicillin, and trimethoprim; Miller et al., 1994). A conservative approach is the recommend use of a second form of contraception while taking a systemic antibiotic agent (Zhanel et al., 1999), but evidence for this is very limited (Miller et al., 1994).

Tetracycline class

Tetracycline treatments, which include minocycline, doxycycline, and tetracycline, are considered first-line therapy in patients with moderate-to-severe inflammatory acne except in certain circumstances including pregnancy, age <8 years, or known allergy. Tetracycline agents have notable anti-inflammatory effects (Zaenglein et al., 2016). Pseudotumor cerebri is a rare phenomenon that is associated with the use of tetracycline agents (Zaenglein et al., 2016).

Tetracycline medications including minocycline and doxycycline are classified as FDA pregnancy category D. Tetracycline agents should not be used during pregnancy because use during the second and third trimester is known to cause discoloration of the teeth and bones. However, there is no firm evidence that first-trimester use is associated with major birth defects (Kong and Tey, 2013; Meredith and Ormerod, 2013). Cases of maternal liver toxicity that is associated with the use of tetracycline agents during the third trimester have been reported (Hale and Pomeranz, 2002; Rothman and Pochi, 1988; Wenk et al., 1981). Although there is a theoretical risk of bone and teeth malformation if tetracycline is administered during lactation, low concentrations of neonatal absorption are expected because of its strong binding with calcium ions in breast milk. Tetracycline is generally considered safe for use during breast feeding (Spencer et al., 2001).

Doxycycline

Doxycycline appears to be effective for patients with AV in the 1.7 to 2.4 mg/kg dose range (Leyden et al., 2013), but for practical purposes, doxycycline is usually administered at 50 to 100 mg twice daily for adult patients with acne. Subantimicrobial dosing of doxycycline (i.e., 20 mg twice daily or 40 mg daily) is also effective in patients with moderate inflammatory acne (Moore et al., 2015; Toossi et al., 2008), which further supports tetracycline's anti-inflammatory properties.

Issues to consider when prescribing doxycycline include the fact that doxycycline is more photosensitizing than minocycline (Zaenglein et al., 2016) and more frequently associated with gastrointestinal disturbances, especially at higher doses (Leyden et al., 2013). To mitigate these side effects, patients should be counseled to use sunscreen lotion and other photoprotective measures to decrease the risk of sunburns, take doxycycline with a meal or a full glass of water, and not take doxycycline less than 1 hour prior to bedtime. Additionally, absorption is decreased with the concomitant intake of iron and calcium. The hyclate version of doxycycline tends to have greater gastrointestinal side effects compared with the monohydrate form. Doxycycline is primarily metabolized by the liver and can be used safely in most patients with renal disease (Zaenglein et al., 2016).

Minocycline

Previously, treatment with minocycline was thought to be superior to doxycycline in reducing *P. acnes* (Strauss et al., 2007). However, a recent Cochrane review found that minocycline was effective to treat patients with AV but was not superior to other antibiotic medications (Garner et al., 2012). Minocycline has been shown to be safe and effective at dose of 1 mg/kg, but no dose response was found for efficacy (Fleischer et al., 2006; Zaenglein et al., 2016). For practical purposes, minocycline is generally dosed at 50 to 100 mg twice daily.

Compared with doxycycline, minocycline tends to have lower rates of gastrointestinal side effects but is associated with tinnitus, dizziness, and pigment deposition within the skin, mucous membranes, and teeth. Minocycline-associated pigmentation is more common in patients who take higher doses for longer periods of time (Zaenglein et al., 2016). Rare, serious, immune-mediated events have also been associated with minocycline including drug-induced hypersensitivity syndrome or a drug reaction with eosinophilia and systemic symptoms, drug-induced lupus, and other hypersensitivity reactions (Kermani et al., 2012; Shaughnessy et al., 2010; Smith and Leyden, 2005; Tripathi et al., 2013; Weinstein et al., 2013).

Macrolides

Macrolide medications including erythromycin and azithromycin have been used in the treatment of patients with acne but recently have fallen out of favor as first-line treatment. Macrolide agents are considered alternative therapy when traditional antibiotic medications cannot be used. As with tetracycline, macrolide has some anti-inflammatory properties but the specific mechanism of action in acne is unknown.

The most common side effect is gastrointestinal disturbances (Zaenglein et al., 2016). Macrolide medications occasionally can cause cardiac conduction abnormalities and rarely cause hepatotoxicity (Zaenglein et al., 2016). Macrolide agents as a class have been classified by AAP as safe during lactation (Kong and Tey, 2013).

Erythromycin

Erythromycin is the traditional oral antibiotic medication of choice when a systemic antibiotic treatment is needed for acne while a patient is pregnant (Hale and Pomeranz, 2002; Koren et al., 1998). Due to increasing bacterial resistance, erythromycin should be combined with a topical preparation such as BP (Meredith and Ormerod, 2013). Due to the differences in absorption, 400 mg erythromycin ethyl succinate produces the same serum levels as 250 mg erythromycin base or stearate. For the erythromycin base, dosing ranges from 250 to 500 mg twice daily. For erythromycin ethyl succinate, dosing ranges from 400 to 800 mg twice daily.

Oral erythromycin is classified as FDA pregnancy category B. Erythromycin is more commonly used during pregnancy to treat

other infections, which resulted in larger retrospective studies on pregnancy outcomes (Romoren et al., 2012). Although erythromycin is largely considered safe for use during pregnancy, reports of fetal cardiac malformation exist (Kallen et al., 2005) and prolonged use has been associated with hepatotoxicity in 10-15% of pregnant patients (Hale and Pomeranz, 2002; McCormack et al., 1977).

Azithromycin

Azithromycin is an azalide antibiotic agent that is derived from erythromycin (Meredith and Ormerod, 2013) and tends to be better tolerated compared with erythromycin (Kong and Tey, 2013). Azithromycin has been studied in varying doses (from 3 times a week to 4 days a month) with varying efficacy in patients with AV and all trials used pulse-dosing regimens (Antonio et al., 2008; Basta-Juzbasic et al., 2007; Innocenzi et al., 2008; Kus et al., 2005; Maleszka et al., 2011; Parsad et al., 2001; Rafiei and Yaghoobi, 2006; Zaenglein et al., 2016).

Trial doses have included 500 mg once daily for 4 consecutive days per month for 2 consecutive months (Babaeinejad et al., 2011; Parsad et al., 2001), 500 mg once daily for 3 days in the first week followed by 500 mg once weekly until week 10 (Maleszka et al., 2011), or 500 mg once daily for 3 consecutive days each week in month 1 followed by 500 mg once daily for 2 consecutive days each week in month 2 and then 500 mg once daily for 1 day each week in month 3 (Kus et al., 2005). One study from 2005 showed that azithromycin is as effective to treat patients with AV as doxycycline (Kus et al., 2005). A more recent, randomized, controlled trial that compared treatment with azithromycin 3 days per month to daily doxycycline showed the superiority of doxycycline (Ullah et al., 2014). As with erythromycin, azithromycin is classified as FDA pregnancy category B.

Trimethoprim sulfamethoxazole

Trimethoprim sulfamethoxazole (TMP/SMX) can be used to treat patients with AV that is recalcitrant to macrolide and tetracycline. Treatment with TMP/SMX and trimethoprim carries serious risks and is used for other infectious disorders, which makes the risk of development of resistance a greater issue. Although a few case reports espouse the efficacy of TMP/SMX in the treatment of patients with acne, one small double-blind study showed that TMP/SMX was as effective as treatment with oxytetracycline (Jen, 1980).

The side effects of TMP/SMX include gastrointestinal upset, photosensitivity, and drug eruptions, the most severe of which is Stevens-Johnson syndrome/toxic epidermal necrolysis (Firoz et al., 2012; Roujeau et al., 1995). Severe eruptions including Stevens-Johnson syndrome/toxic epidermal necrolysis are more common in patients with HIV.

Rarely, TMP/SMX can cause serious blood dyscrasias such as neutropenia, agranulocytosis, aplastic anemia, and thrombocytopenia, especially if taken as a long-term therapy, which warrants periodic monitoring with a complete blood cell count testing (Zaenglein et al., 2016). According to the AAD working group, TMP/SMX should be restricted to patients who are unable to tolerate tetracycline agents or in patients who are treatment-resistant (Zaenglein et al., 2016). The usual dosing for patients with AV is one double-strength tablet twice daily.

TMPS/SMX is classified as FDA pregnancy category C. The use of TMP/SMX during the first trimester of pregnancy can lead to folic acid deficiency, which may in turn result in neural tube defects, structural malformations of the cardiovascular and urinary system, and cleft lip or palate (Ho and Juurlink, 2011). These risks are increased among women who do not use a multivitamin that contains folic acid (Hernandez-Diaz et al., 2000).

Additionally, exposure during the third trimester of pregnancy is small for gestational age infants as well as associated with hyperbilirubinemia (Ho and Juurlink, 2011). Both AAP and LactMed consider TMP/SMX safe for use during lactation except when the baby is premature, has severe jaundice, or has G6PD deficiency, during which there is a higher risk of kernicterus (Kong and Tey, 2013).

Penicillin and cephalosporin

Penicillin and cephalosporin are well established as safe for use during pregnancy and lactation (Hale and Pomeranz, 2002). However, they are rarely used to treat patients with acne because information with regard to efficacy is sparse. Penicillin and cephalosporin can be used as an alternative to conventional antibiotic medications, especially during pregnancy or with allergies to other classes of antibiotic treatments (Zaenglein et al., 2016). Side effects include risk of hypersensitivity reactions that range from mild drug eruptions to anaphylaxis and gastrointestinal disturbances (i.e., nausea, diarrhea, and abdominal distention and discomfort; Zaenglein et al., 2016). The recommended dosing for amoxicillin is 250 mg twice daily up to 500 mg three times daily.

Cephalosporin has in vitro activity against *P. acnes*, but as a class, cephalosporin treatment is hydrophilic and thought to poorly penetrate microcomedones in vivo (Mays et al., 2012). A retrospective study of 93 patients showed that cephalexin is effective to treat patients with acne; 78% of patients experienced clinical improvement with a dosing regimen of 500 mg twice daily (Fenner et al., 2008).

Isotretinoin

Isotretionoin is an important nonhormonal and nonantimicrobial treatment option for adult women with acne (Gollnick et al., 2003). Oral isotretinoin is FDA-approved for the treatment of severe recalcitrant AV but can also be used to treat patients with moderate acne that is either treatment-resistant or relapses quickly after discontinuation of oral antibiotic therapy (Agarwal, et al., 2011; Akman et al., 2007; Borghi et al., 2011; Choi et al., 2011a, b; Kaymak and Ilter, 2006; Lee et al., 2011). Several studies have shown that isotretinoin effectively decreases sebum production, the number of acne lesions, and acne scarring (Amichai et al., 2006; Chivot and Midoun, 1990; Goldstein et al., 1982; Goulden et al., 1997a, b; Jones et al., 1983; King et al., 1982; Layton et al., 1993; Lehucher-Ceyrac and Weber-Buisset, 1993; Lester et al., 1985; Peck et al., 1982; Rubinow et al., 1987; Stainforth et al., 1993; Strauss and Stranieri, 1982, Strauss et al., 1984). According to the AAD working group, isotretinoin is also indicated for the treatment of patients with moderate inflammatory acne that is either treatment-resistant or produces physical scarring or significant psychosocial distress (Zaenglein et al., 2016).

Isotretinoin is usually initiated at a starting dose of 0.5 mg/kg/day for the first month and then increased to 1 mg/kg/day as tolerated with a goal of a cumulative dose of between 120 and 150 mg/kg (Goldsmith et al., 2004; Layton et al., 1993; Lehucher-Ceyrac et al., 1999). In very severe cases, lower initial doses in addition to oral corticosteroid medications may be needed. However, more recent studies have demonstrated that higher cumulative doses that exceed 200 mg/kg may be more effective to reduce the rates of acne relapse and retreatment (Coloe et al., 2011; Zeitany et al., 2016).

Low-dose isotretinoin (0.25-0.4 mg/kg/day) and lower cumulative dose regimens may be used to minimize the side effects that are associated with systemic retinoid therapy and thereby lead to improved tolerability and increased patient satisfaction (Agarwal et al., 2011; Akman et al., 2007; Amichai et al., 2006; Choi et al., 2011a, b; De and Kanwar, 2011; Lee et al., 2010; Rademaker, 2010). However, intermittent dosing is not as effective as daily dosing and exhibits higher relapse rates (Agarwal, et al., 2011; Akman et al.,

2007; Choi et al., 2011a, b; King et al., 1982). Absorption of isotretinoin is increased with fatty foods and isotretinoin is recommended to be taken with meals (Strauss et al., 2001; Webster et al., 2013). The lidose formulation (Absorica) has absorption profiles that are not dependent on fat intake.

In the treatment of adult women, serious considerations should be given to isotretinoin's potential teratogenicity. In addition, side effects are numerous, including xerosis, cheilitis, xerophthalmia, decreased night vision, vision changes, headache, hepatotoxicity, hypertriglyceridemia, mood changes, bone demineralization, cardiovascular risk factors, possible link to depression/anxiety/mood changes/suicidality, and possible link to inflammatory bowel disease (IBD). With regard to the association of isotretinon with IBD, the position of the AAD is that "current evidence is insufficient to prove either an association of causal relationship between isotretinoin use and IBD" (Zaenglein et al., 2016). The most prevalent side effects of isotretinoin mimic symptoms of hypervitaminosis A (Zaenglein et al., 2016). With standard dosing, these side effects resolve after discontinuation of therapy (Zaenglein et al., 2016).

Data with regard to an evidence-based link between isotretinoin and depression, anxiety, mood changes, or suicidal ideation/suicide is mixed. Although many small case reports and series show that isotretinoin has no negative effect on mood, memory, attention, or executive function (Alhusayen et al., 2013; Bozdag et al., 2009; Chia et al., 2005; Cohen et al., 2007; Etminan et al., 2013; Hull et al., 1991; Jick et al., 2000; Kaymak and Ilter, 2006; Marqueling and Zane, 2007; Nevoralova and Dvorakova, 2013; Ormerod et al., 2012; Rashtak et al., 2014; Rehn et al., 2009; Rubinow et al., 1987; Zaenglein et al., 2016), the FDA presented 40 cases that showed that isotretinoin dechallenge and rechallenge was associated with psychiatric symptoms (U.S. Food and Drug Administration, 2003). In the FDA case series, patients recovered after isotretinoin was discontinued and had a recurrence of symptoms after reinitiating isotretinoin. Of these patients, 75% had no reported prior psychiatric history before isotretinoin therapy and the median time to recovery after discontinuation of isotretinoin was 4.5 days, which is consistent with the half-life of isotretinoin and its metabolites. When patients were rechallenged, the time to onset of the psychiatric symptoms was on average shorter, and 10 patients had persistent psychiatric symptoms after isotretinoin discontinuation. As of December 31, 2001, 140 isotretinoin users worldwide have committed suicide while taking isotretinoin or within a few months of discontinuation of treatment and another 257 patients have been hospitalized for severe depression or attempted suicide (Duenwald, 2002). However, some have argued that the number of reported cases of depression among isotretinoin users is no greater than in the general population (Lamberg, 1998). The AAD working group recommends that prescribing physicians monitor patients for any indication of depressive symptoms and educate patients on the potential risks of treatment with isotretinoin.

Laboratory test result monitoring for patients on isotretinoin varies widely among practitioners. Serum cholesterol, triglycerides, and transaminases are known to increase in some patients who take oral isotretinoin (Bershad et al., 1985; De Marchi et al., 2006; Zech et al., 1983). Routine monitoring of serum lipid profiles and liver function studies are recommended to be done regularly but the interval varies (Bershad et al., 1985; Lammer et al., 1985; Leachman et al., 1999; McElwee et al., 1991; Zech et al., 1983). Some practitioners monitor laboratory test results monthly, but others only check at baseline and after dosing changes.

Hansen et al. (2016) recommend that in healthy patients with normal baseline lipid panel and liver function test results, repeated studies should be performed after 2 months of isotretinoin therapy. If the findings are normal, no further testing may be required. The AAD working group did not find any evidence-based reason to warrant routine monitoring of complete blood cell counts (Zaenglein et al., 2016). Pregnancy testing is required for female patients of childbearing potential at baseline, monthly during therapy, and 1 month after completion of isotretinoin treatment.

The use of oral isotretinoin during pregnancy is absolutely contraindicated (FDA pregnancy category X) due to its known severe teratogenicity including craniofacial, cardiac, and thymic malformations (Lammer et al., 1985). As a result of these serious effects, the manufacturers of oral isotretinoin have developed pregnancy prevention programs where preferably two forms of contraception are recommended (Goodfield et al., 2010). Currently, the United States and United Kingdom require enrollment in these pregnancy prevention programs to receive oral isotretinoin.

In the United States, the FDA established the iPLEDGE program in 2006. Dermatologists should counsel women that they should not become pregnant 1 month before, during, or within 1 month after completion of isotretinoin therapy. However, in a recent survey study of women who were sexually active during isotretinoin therapy, 29% admitted to noncompliance with the iPLEDGE pregnancy prevention requirements (Collins et al., 2014).

Miscellaneous and adjuvant therapies

The following therapies have limited evidence for their efficacy in the treatment of patients with AV. However, these treatments may improve patients' appearance and be helpful as part of an overall AV treatment regimen. Some of these modalities may be helpful to treat acne scarring as well. These treatments include comedo extraction (Meredith and Ormerod, 2013; Zaenglein et al., 2016), cryotherapy (Fox et al., 2016), electrocauterization (Fox et al., 2016), chemical peels (Dreno et al., 2011; Grover and Reddu, 2003; Ilknur et al., 2010; Kempiak and Uebelhoer, 2008; Levesque et al., 2011; Meredith and Ormerod, 2013; Ramos-e-Silva et al., 2015; Zaenglein et al., 2016; including glycolic acid Atzori et al., 1999; Grover and Reddu, 2003; Ilknur et al., 2010, SA Levesque et al., 2011, and retinoic acid Ramos-e-Silva et al., 2015), microdermabrasion (Karimipour et al., 2010; Kempiak and Uebelhoer, 2008; Lloyd, 2001; Ramos-e-Silva et al., 2015; Tan et al., 2001), laser treatment (Zaenglein et al., 2016; including pulsed dye, potassium titanyl phosphate, fractionated CO_2, fractionated and nonfractionated infrared, radiofrequency, and intense pulsed light), photodynamic therapy (Barbaric et al., 2016; Gold et al., 2004; Kong and Tey, 2013; Ma et al., 2013; Nast et al., 2012; Pollock et al., 2004; Ross, 2005; Sakamoto et al., 2010; Wang et al., 2010; Zaenglein et al., 2016 including blue-violet light phototherapy and red light phototherapy), narrow-band ultraviolet B phototherapy (Meredith and Ormerod, 2013; Ross, 2005; Zeichner, 2011), intralesional triamcinolone acetonide (Levine and Rasmussen, 1983; Potter, 1971), surgical techniques (Jacob et al., 2001; Ramos-e-Silva et al., 2015; Sanchez Viera, 2015 including punch excision and subcision), and filler (Jacob et al., 2001; Sanchez Viera, 2015).

Complementary and alternative therapies

Many patients wish to use more natural treatments and may look to herbal and alternative agents for treatment. Although most of these agents are generally well tolerated, there are limited data with regard to efficacy and safety. Additionally, the specific ingredients, concentrations, and potential adulteration with other unwanted chemicals is not well regulated and sometimes cannot be confirmed. These complementary and alternative therapies include tea tree oil (Bassett et al., 1990; Bowe and Shalita, 2008; Enshaieh et al., 2007; Hammer, 2015; Sharquie et al., 2006), niacinamide (Draelos et al., 2006; Fox et al., 2016; Gehring, 2004; Namazi, 2007), ayurvedic compounds (Lalla et al., 2001; Paranjpe and Kulkarni, 1995), barberry extract (Fouladi, 2012), gluconolactone (Hunt and Barnetson, 1992),

antioxidant agents (Sardana and Garg, 2010), zinc (Dreno and Blouin, 2008; Gupta et al., 2014; Meredith and Ormerod, 2013; Nast et al., 2012; Sardana and Garg, 2010; Strauss et al., 2007), probiotic treatments (Jung et al., 2013), fish oil (Khayef et al., 2012), green tea (Gaur and Agnihotri, 2014; Mahmood et al., 2010; Zaveri, 2006), basil oil (da Silva et al., 2012), copaiba oil (da Silva et al., 2012), minerals (Gupta et al., 2014; Ma'or et al., 2006; Park et al., 2009), resveratrol (Docherty et al., 2007; Fabbrocini et al., 2011; Simonart, 2012), rose water (rosa damascena; Hajhashemi et al., 2010), seaweed (Capitanio et al., 2012; Choi et al., 2011a, b), taurine bromamine (Marcinkiewicz, 2010; Marcinkiewicz et al., 2006, 2008), dietary modification (Adebamowo et al., 2005, 2006; Bhate and Williams, 2013; Di Landro et al., 2012; Ismail et al., 2012; Strauss et al., 2007; Zaenglein et al., 2016), biofeedback-assisted relaxation (Hughes et al., 1983), cognitive imagery (Hughes et al., 1983), and acupuncture (Kim and Kim, 2012).

Other complementary and alternative medicines (Fox et al., 2016) include *Achillea millefolium*, amaranth, antimicrobial peptides, arnica, asparagus, bay, benzoin, birch, bittersweet nightshade, black cumin, black walnut, borage, Brewer's yeast, burdock root, calendula, celandine, chamomile, chaste tree, *Commiphora mukul*, capaiba oil, coriander, cucumber, duckweed, DuZhong extract, English walnut, *Eucalyptus dives*, fresh lemon, garlic, geranium, grapefruit seeds, jojoba oil, juniper twig, labrador tea, lemongrass, lemon, neem, oak bark, onion, orange peel, orange, Oregon grape root, patchouli, pea, petitgrain, pine, pomegranate rind extract, poplar, pumpkin, rose myrtle, rhubarb, rosemary, rue, safflower oil, sandalwood, soapwort, *Sophora flavescens*, specific antibodies, stinging nettle, sunflower oil, *Taraxacum officinale,* thyme, turmeric, vinegar, vitex, witch hazel, *Withania somnifera*, and yerba mate extract.

Novel therapies

New therapies to treat patients with AV continue to be developed. The newest agents include minocycline foam, topical nitric oxide-releasing agent, and cortexolone 17α-propionate. Many of these new therapies are in various stages of testing, and although the ultimate efficacy is difficult to predict, preliminary studies show promising results.

Minocycline foam

Oral minocycline has been shown to be effective in the treatment of patients with AV; however, systemic side effects including abnormal mucocutaneous pigmentation and autoimmune reactions may limit its use (Kircik, 2010; Smith and Leyden, 2005). A recent phase 2, prospective, multicenter, randomized, double-blind, dose finding study on topical minocycline 4% foam was conducted and showed a significant reduction from baseline in lesion count versus vehicle at 12 weeks for both inflammatory (71.1% vs. 50.5%; $p = 0.0001$) and noninflammatory lesions (72.7% vs. 56.5%; $p = 0.0197$; Shemer et al., 2016). The significant reduction in lesions were observed as early as week 3 and persisted until the end of the study at week 12. Treatment was well tolerated and safe with no drug-related systemic side effects or serious adverse events. Minocycline 4% foam will be further evaluated in phase 3 trials (Shemer et al., 2016).

Topical nitric-oxide

P. acnes is known to induce the production of interleukin-1 cytokines and contribute to the pathogenesis of acne. Nitric oxide (NO) has been shown to have broad-spectrum antimicrobial, wound-healing, and immunomodulatory properties (Friedman and Friedman, 2009; Martinez et al., 2009; Qin et al., 2015). Qin et al. (2015) showed that *P. acnes* is highly sensitive to NO and human keratinocyte, monocyte, and embryonic zebra fish assays did not reveal cytotoxicity.

In a recent phase 2, randomized, double-blind, placebo-controlled, three-armed study, a topical NO-releasing drug at 1% and 4% had a significantly greater mean percent reduction in noninflammatory lesions and patients who were treated with the 4% concentration had a significantly greater mean percent reduction in inflammatory lesion count at week 12 (Baldwin et al., 2016). Both concentrations were safe and well-tolerated by patients.

Topical cortexolone 17α-propionate 1% cream

Systemic anti-androgens such as spironolactone and combination oral contraceptive medications can be used in the effective treatment of patients with AV (Kong and Tey, 2013; Meredith and Ormerod, 2013; Thiboutot and Chen, 2003; Zaenglein et al., 2016). However, systemic use of anti-androgens is limited to women who wish to conceive or have other endocrine disorders or contraindications (Chen et al., 1995). A topical anti-androgen treatment has not been made available for use to date.

Cortexolone 17α-propionate is a steroidal antiandrogen agent that has strong antiandrogen activity and mild anti-inflammatory properties (Celasco et al., 2004). Cortexolone 17α-propionate competitively inhibits endogenous androgen binding at the human androgen receptor level without inhibiting the skin 5α-reductase (Celasco et al., 2004; Trifu et al., 2011). The agent is quickly metabolized once it penetrates the epidermis and frees inactive cortexolone; therefore, cortexolone 17α-propionate does not have systemic antiandrogenic effects (Trifu et al., 2011).

In a pilot randomized, double-blind, comparative study of cortexolone 17α-propionate versus placebo versus tretinoin 0.05% cream, cortexolone 17α-propionate 1% cream was well tolerated by patients and performed significantly better than placebo with regard to reductions in total lesion count, inflammatory lesion count, and acne severity index. Cortexolone 17α-propionate 1% cream was also clinically more effective than tretinoin 0.05% cream but this difference was not statistically significant.

Conclusions

A myriad of treatment choices is available to treat adult female patients with acne. Treatment options should be tailored to the individual patient with considerations for the patient's preferences, tolerability of the agent, and psychosocial factors. A relatively limited number of options are available for the management of acne during pregnancy and lactation. However, the level of evidence on the safety of any therapies during pregnancy and lactation is low. Novel agents continue to be developed to treat patients with AV, which will further enhance the clinician's care of patients with this impactful and prevalent disease.

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