Acne Vulgaris

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LEARNING OBJECTIVES

1. Apply current guidelines to the management of acne in the pediatric population.
2. Given a patient's signs and symptoms, classify the level of acne severity.
3. Evaluate the advantages and disadvantages of drug therapy options for acne.
4. Justify the use of prescription and nonprescription products in a patient-specific treatment plan.

ABBREVIATIONS IN THIS CHAPTER

AAD	American Academy of Dermatology
AAP	American Academy of Pediatrics
AV	Acne vulgaris
COC	Combined oral contraceptive
EDF	European Dermatology Forum
OAB	Oral antibiotic
TAB	Topical antibiotic
TR	Topical retinoid

Table of other common abbreviations.

Note
The American Academy of Dermatology released its updated 2016 *Guidelines of Care for Acne Vulgaris Management* after this chapter went to print. Please visit: https://www.aad.org/practice-tools/quality-care/clinical-guidelines/acne for more information

INTRODUCTION

Background

Acne vulgaris (AV) is a commonly diagnosed inflammatory skin condition that affects pediatric and adult patients. Although traditionally viewed as an adolescent condition (it develops in almost 90% of patients starting at age 12 years), patients as young as 8 years can present with AV, and the condition can persist into adulthood (up to an average age of 45). Adolescent patients have reported low self-esteem and symptoms of depression leading to a lower quality of life (Bhate 2013). Psychological comorbidities, including depression and anxiety, have largely been associated with AV, but it is unclear whether AV is the cause or only worsens the preexisting conditions (Barnes 2012). The potential for hyperpigmentation and scarring into adulthood affects later quality of life as well (Gieler 2015). Thus, more patients are presenting to health care providers seeking treatment.

This chapter focuses on the updates related to AV management, the significance of appropriate treatment, and the role of the ambulatory care pharmacist in assisting with management.

Pathophysiology

The pathology of AV is multifactorial and stems from excess sebum production, skin keratinization changes, *Propionibacterium acnes*, and inflammatory processes. In pediatric patients, acne development may result from endocrine changes brought about by the onset of puberty, increased androgenic hormones, and increased sebum production.

Acne vulgaris primarily results from the overproduction of oils in the sebaceous follicles of the skin, which are heavily found around the face and upper back. Alterations to follicular development, including hyperkeratinization, contribute to acne development. The gram-positive anaerobe *P. acnes* inhabits the skin and sebaceous follicles. *P. acnes* releases enzymes (e.g., lipases, proteases) that are responsible for the AV-associated inflammation and the creation of inflammatory mediators. These inflammatory mediators subsequently cause plugged follicles to become inflamed, thus leading to the inflammatory lesions known as papules, pustules, and nodules. New studies have found that various other inflammatory mediators (e.g., interleukin-1, matrix metalloproteinases) also play a role in acne pathogenesis. These aspects of innate immunity may be the targets for the future development of therapeutic agents (Dreno 2015; Das 2014).

Endocrine abnormalities such as those found during pregnancy or in polycystic ovarian syndrome in women of reproductive age may also lead to acne, regardless of medical history. One of the clinical characteristics of polycystic ovarian syndrome is hyperandrogenism, which increases sebum production and subsequent acne formation. These patients often have acne lesions not only on their faces, but also on their neck, chest, and upper back, where sebaceous glands are also prevalent (Archer 2004). Sebaceous glands also respond to other hormones such as the corticotrophin-releasing hormone, which increases as a result of stress (Nast 2012).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Specific pathophysiology and inflammatory processes associated with acne development
- General knowledge of topical and oral agents used to treat acne

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Eichenfield LF, Krakowski AC, Piggott C, et al. American Acne and Rosacea Society. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics 2013;131(suppl 3):S163-86.
- Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol 2007;56:651-63.

Table of common laboratory reference values.

Box 1-1. Drugs Commonly Associated with Acne

- Anabolic steroids
- Cetuximab
- Corticosteroids
- Cyclosporine
- Halogens
- Hormonal contraceptives (high in androgenic properties)
- Isoniazid
- Lithium
- Phenytoin
- Vitamin B_{12}

Information from: Valeyrie-Allanore L, Sassalos B, Roujeau J. Drug-induced skin, nail, and hair disorders. Drug Saf 2007;30:1011-30; and Du-Thanh A, Kluger N, Bensalleh H, et al. Drug-induced acneiform eruption. Am J Clin Dermatol 2011;12:233-45.

Acne vulgaris may be secondary to drug use (Box 1-1). Drug-induced acne typically manifests as inflammatory lesions, with rarely any evidence of comedones (Figure 1-1). Moreover, the sudden appearance of acne may be found outside the usual sebaceous-filled areas. Drug-induced acne should be part of the differential if the patient recently started a new medication and has no prior history of AV, or if standard pharmacotherapy is not effective in treating the acne (Du-Thanh 2011; Valeyrie-Allanore 2007).

Goals of Therapy

Goals of therapy for all patients, regardless of age, are the same: (1) successfully target and resolve the underlying

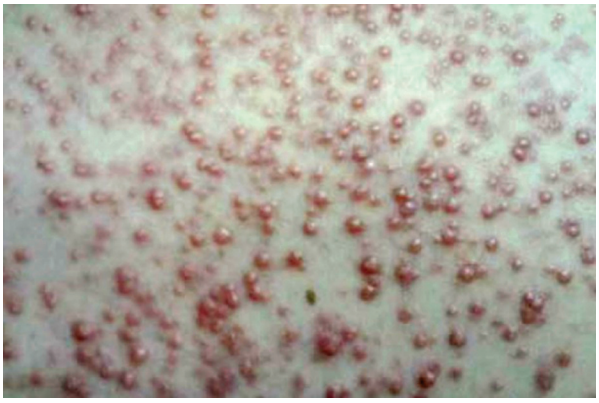

Figure 1-1. Drug-induced acne. Presentation includes inflammatory lesions (papules and pustules) and lack of comedones.

Image reprinted from: U.S. National Library of Medicine Open Access Biomedical Image Search Engine [homepage on the Internet].

pathology of AV; and (2) reduce inflammatory lesions, thereby reducing and preventing scarring. The European Dermatology Forum (EDF) guidelines suggest that a 10% reduction in the number of lesions is considered clinically successful, but ultimately, the patient perspective on success varies (Nast 2012). Finally, the patient's quality of life (e.g., reduced psychosocial stressors) is expected to improve.

CLASSIFICATION OF ACNE SEVERITY

Although there is no standardized staging system, an understanding of acne and its presentation can assist the pharmacist in determining its severity and thus the appropriate treatment. Acne can manifest as comedones in open form, closed form, or both. Microcomedones (Figure 1-2) serve as precursors to comedones, when follicles begin to be inhabited by a mixture of sebum, bacteria, and keratinized cells. When this mixture accumulates to plug the follicle, a comedone is produced and is considered the closed form, also known as a whitehead. If the follicular duct's buildup increases, keratin buildup on the skin exposed to air results in the open comedone, also known as a blackhead. The bacteria *P. acnes* colonizes within the follicle and is responsible for the development of inflammation.

Inflammatory lesions (Figure 1-3) may further be classified as papules, pustules, or nodules. A papule occurs when there is a break in the follicular wall, causing white blood cells to amass. A pustule later forms when the white blood cells reach the surface of the skin; this is commonly known as the pimple. When the inflamed follicle erupts along the bottom, a large, inflamed nodule results. If the lesion is filled with a large amount of pus, a severe inflammatory reaction can occur to form a cyst. Inflammatory lesions can be painful and potentially lead to permanent scarring, underlining the importance of appropriate treatment, which varies depending on the type of lesions.

Acne severity can generally be categorized into mild, moderate, or severe stages. Guidelines endorse the use of these stages in slightly different ways, depending on the type of acne (i.e., lesions or comedones), the quantity, or both. Two studies note that various grading systems exist, but no consensus is available (Nast 2012; Strauss 2007) (Table 1-1).

A mild case of AV is primarily noninflammatory and comedone based, but both patients and clinicians may perceive a large quantity of comedones as a moderate or severe case. Thus, it is important to be patient-specific when classifying

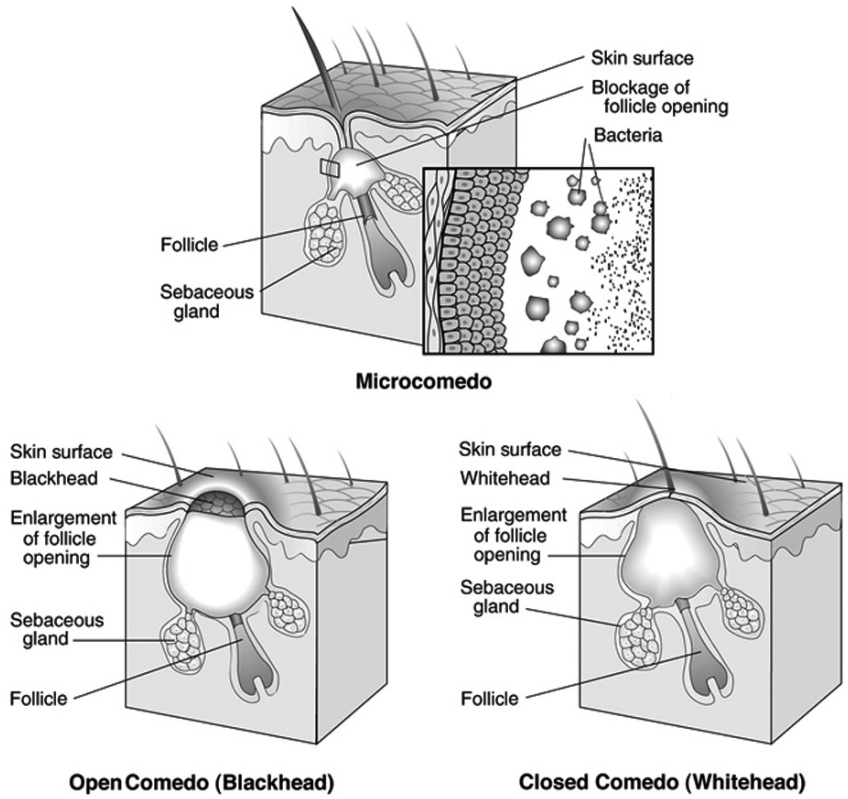

Figure 1-2. Microcomedo, closed comedo (whitehead), and open comedo (blackhead).

Images reprinted from: National Institute of Arthritis and Musculoskeletal and Skin Diseases [homepage on the Internet].

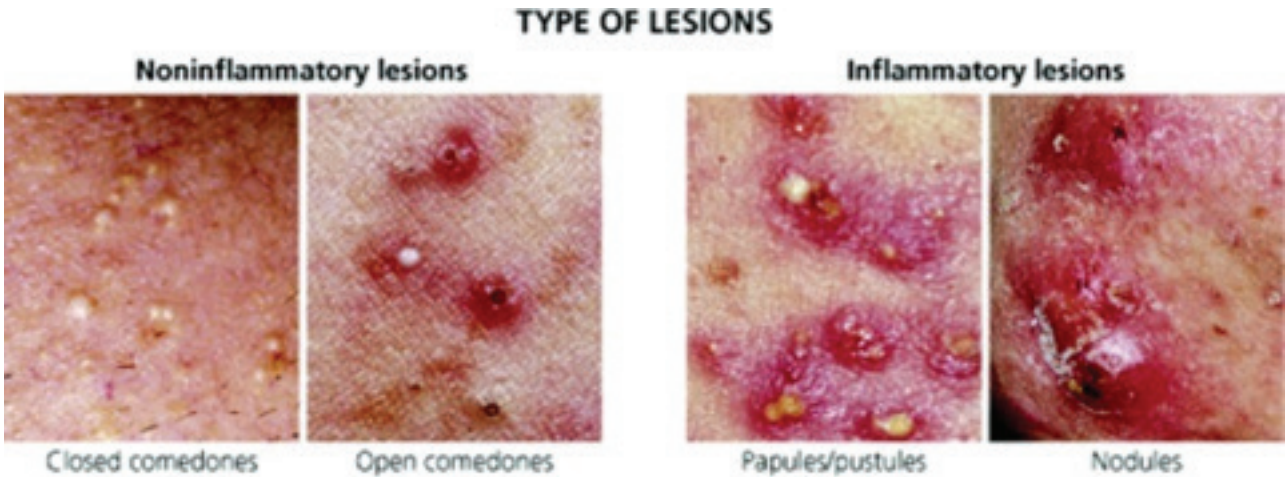

Figure 1-3. Noninflammatory versus inflammatory lesions.

Images reprinted from: National Institute of Arthritis and Musculoskeletal and Skin Diseases [homepage on the Internet].

AV to determine the most effective, patient-specific treatment. Patients presenting with inflammatory lesions are generally classified as having moderate or severe acne. Conglobate acne, as defined by the EDF treatment guidelines, is the most severe form of acne; it is characterized by a mix of grouped comedones and inflammatory papules and nodules. This type of acne, though rare, is most often found in adult men, and the inflammatory lesions manifest primarily

Table 1-1. Comparison of Severity Classification of Acne

		Guideline		
General Classification	AAD[a]	Global Alliance	EDF	AAP
Mild	—	Comedonal or mixed and papular/ pustular	Comedonal or mild to moderate papulopustular	Comedonal or inflammatory/mixed lesions
Moderate	—	Mixed and papular/ pustular or nodular	Mild to moderate papulopustular	Comedonal or inflammatory/mixed lesions
Severe	—	Nodular or conglobate	Severe papulopustular/ moderate nodular or severe nodular/ conglobate	Inflammatory/mixed and/or nodular lesions

[a]Not given.

AAD = American Academy of Dermatology; AAP = American Association of Pediatrics; EDF = European Dermatology Forum.

Information from: Thiboutot D, Gollnick H, Bettoli V, et al; Global Alliance to Improve Outcomes in Acne. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne Group. J Am Acad Dermatol 2009;60(suppl 5):S1-50; Nast A, Dréno B, Bettoli V et al; European Dermatology Forum. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol 2012;26(suppl 1):1-29; and Eichenfield LF, Krakowski AC, Piggott C, et al; American Acne and Rosacea Society. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics 2013;131(suppl 3):S163-86.

on the trunk and upper limbs and less so on the face (Nast 2012).

One study in adolescents and adults classified AV into four groups: comedonal acne, mild-moderate papulopustular acne, severe papulopustular acne/moderate nodular acne, and severe nodular acne/conglobate acne (Nast 2012).

CLINICAL GUIDELINE UPDATES IN MANAGEMENT OF AV

Management of Acne in the Pediatric Population

The American Academy of Pediatrics (AAP) published its first guidelines for the management of AV in 2013. The guidelines categorize pediatric AV by age groups and have recommendations for diagnosis in each group: neonatal (birth to 6 weeks), infantile (6 weeks to 1 year), mid-childhood (1–7 years), pre-adolescent (7–12 years or before menarche in girls), and adolescent (12–19 years or after menarche in girls). Acne across each group is generally self-limiting and may present in various ways, depending on the age. When hormonal abnormalities are suspected, a referral for an endocrine workup is required.

Neonatal acne may present in the form of papulopustular conditions, without comedones. Neonates rarely have androgen-triggered comedonal and inflammatory acne. Infantile acne is more common in boys, presenting in the form of both noninflammatory and inflammatory lesions. Because mid-childhood acne is rare, the pathology may be endocrine in nature. However, with evidence indicating that more girls have menarche at younger ages, it is not uncommon to see acne development in the pre-adolescent age group. Like adolescents, pre-adolescents commonly present with comedones around the "T-zone" (the forehead and center of the face). However, if the patient also has signs of polycystic ovarian syndrome or other endocrine abnormalities, an endocrine workup may be warranted. The provider working through the differential should consider the patient's physical findings and age. The evidence behind recommendations related to diagnosis is still limited, with most recommendations given a Strength of Recommendation Taxonomy (SORT) grade C (Ebell 2004), which is primarily based on consensus or disease-oriented evidence (Eichenfield 2013).

Overall, there are very few differences in AV treatment between the pediatric and adult populations, according to AAP. Treatment approach and options are discussed later in this chapter.

Updates on the Management of Acne in the Adult

The most recent American Academy of Dermatology (AAD) guidelines for the management of AV were published in 2007. Instead of providing a specific acne classification, the authors recommend the use of any grading system to determine the best form of treatment. The guidelines focus on the level of evidence behind each treatment option (Strauss 2007). Clinical updates are under way and expected to be published in the near future. Updates will likely address limiting the duration of antibiotic use, with a focus on maximizing other available therapies (Bowers 2015).

The most recent Global Alliance to Improve Outcomes in Acne Group publication was released in 2009. Compared with its original 2003 guidelines, the new release contains more evidence associated with acne pathophysiology, the significance of combination therapies, and the role of light and laser therapy (Thiboutot 2009).

The EDF's evidence-based guidelines, first published in 2012, used a systematic analysis to review the literature and develop their recommendations. Although these guidelines do not address the place of OTC products in therapy, they mention benzoyl peroxide. Another limitation is that they highlight only the treatment options available in Europe. In addition, their recommendations are focused on the treatment of facial acne, whereas other guidelines do not explicitly state a focus of body area. Consistent with reports by other existing guidelines, microbial resistance is prevalent in Europe as well, and the use of antibiotics for a limited duration is highly recommended (Nast 2012).

Across all guidelines, the approach to therapy according to severity is similar and is discussed in the following.

NONPRESCRIPTION DRUG THERAPY OPTIONS FOR ACNE

Patients often initially choose OTC products for help in clearing up their acne. The various OTC product forms include facial washes, creams, and pads; their primary active ingredients are benzoyl peroxide, salicylic acid, sulfur, sodium sulfacetamide, and resorcinol. This class of products is generally helpful for patients with mild acne (Table 1-2).

FDA Alert Regarding OTC Products

In 2014, the FDA released a report to consumers and health care providers regarding the serious, potentially life-threatening allergic skin reactions associated with the use of OTC products used to treat AV. The report specifically mentions any topical product containing benzoyl peroxide or salicylic acid; it is unclear, given the reports, whether the adverse reactions occur because of these specific active ingredients or because of the product's respective inactive ingredients. Moreover, these products have various formulations and brand names.

Although the reported reactions did not result in death, 44% required hospitalization and 38% consisted of severe hypersensitivity reactions (e.g., shortness of breath, swelling around facial features).

Although not mandated, the FDA has encouraged manufacturers of these OTC products to revise their drug labels to communicate these findings to consumers. Patients should be educated about the potential for severe allergic reactions

Table 1-2. Comparison of Available OTC Therapies

	Benzoyl Peroxide	Salicylic Acid	Sulfur	Resorcinol
Properties				
• Comedolytic	✓	✓	✓	
• Keratolytic	✓	✓	✓	✓
• Antibacterial	✓	✓	✓	✓
• Anti-inflammatory	✓	✓		
Available concentrations	2.5%–10%	0.5%–2%	2%–10%	2% 3%–8%[a]
Dosing frequency	Once to three times daily, depending on formulation			
Limitations/adverse effects	May bleach hair and clothing, photosensitivity	Burning, stinging, skin discoloration	Odor	Skin hyperpigmentation, irritation
	Potentially life-threatening allergic reactions	Potentially life-threatening allergic reactions		
	Dryness, erythema, skin irritation	Dryness, erythema, skin irritation	Dryness, erythema, skin irritation	Dryness, erythema, skin irritation

[a]Available in combination products with sulfur.

Information from: FDA Drug Safety Communication: FDA warns of rare but serious hypersensitivity reactions with certain over-the-counter topical acne products. Safety Announcement. June 2014; Eichenfield LF, Krakowski AC, Piggott C, et al; American Acne and Rosacea Society. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics 2013;131(suppl 3):S163-86; Decker A, Graber EM. Over-the-counter acne treatments. J Clin Aesthet Dermatol 2012;5:32-40; Gupta AK, Nicol K. The use of sulfur in dermatology. J Drugs Dermatol 2004;3:427-31; and Del Rosso JQ. The use of sodium sulfacetamide 10%-sulfur 5% emollient foam in the treatment of acne vulgaris. J Clin Aesthetic Dermatol 2009;2:26-9.

and warned to discontinue the product if these reactions occur. In addition, as with many other topical products, it has been suggested that on first use of these products, a small amount should be applied to a small affected area for 3 days, and if no reactions occur, patients may continue use to manage their acne (FDA 2015).

Benzoyl Peroxide

Of the available OTC products, benzoyl peroxide is the most studied and commonly used. This agent has properties that can target AV's multifactorial pathology, and its lipophilicity allows penetration into the skin and effective facilitation of its antibacterial properties without incurring antimicrobial resistance. In addition, benzoyl peroxide has keratolytic, comedolytic, and mild anti-inflammatory properties.

Benzoyl peroxide is a topical agent that comes in various forms, including creams, gels, pads, and bars. Its drying effects are dose-dependent, so the initial application should use the lowest concentration dosed once every other day. If tolerated, the patient may titrate to daily use or more than one application daily. If irritation is an issue, an emollient vehicle can be considered (Eichenfield 2013). Limited studies have shown that the efficacy of 10% benzoyl peroxide (as assessed by a reduction in the number of lesions or reduction in free fatty acids) is not necessarily better than 5%, or even 2.5%; however, higher concentrations result in more irritation and drying effects (Brandstetter 2013).

Otherwise, the FDA recognizes benzoyl peroxide as a generally safe and effective medication (Fed Regist 2010). Patients should be informed that it will take about 4–8 weeks to notice any improvement. Patients should avoid its contact with eyes, lips, and mouth. In addition, benzoyl peroxide can bleach the hair and clothing. Because photosensitivity is a concern, patients should apply sunscreen. The most common adverse effects include skin dryness and irritation. There are few limitations to using benzoyl peroxide, other than its adverse effects, which are transient with prolonged use. However, according to the previously discussed FDA statement, patients should monitor for signs of a severe allergic skin reaction (FDA 2015).

Benzoyl peroxide may be used as monotherapy in mild comedonal acne or in combination with topical retinoids (TRs) in mild to moderate mixed acne. When benzoyl peroxide is used in combination with TRs, the agents should be applied separately a few hours apart because of their instability to light when mixed together. The only exception to this is adapalene, which can be used together with benzoyl peroxide because of adapalene's greater stability in light (Thielitz 2008). Benzoyl peroxide is beneficial as an add-on agent in patients using topical antibiotics (TABs) to reduce antibacterial resistance and improve efficacy (Eichenfield 2013; Thiboubout 2009; Strauss 2007).

Salicylic Acid

Salicylic acid, another common active ingredient in topical OTC products advertised to treat AV, is found in creams, gels, scrubs, lotions, pads, and liquid washes. Salicylic acid has mild anticomedonal properties and has been found effective in reducing inflammatory lesions and open comedones (although less so than benzoyl peroxide or TRs) in mild forms of acne (Decker 2012).

Similar to benzoyl peroxide, salicylic acid is an option for mild to moderate inflammatory acne. Other than mild skin irritation and dryness, it is well tolerated. Because of reports of burning and stinging, however, contact should be avoided in the eyes and other mucous membranes. Salicylic acid may cause skin discoloration, particularly in darker-skinned patients. Counseling on salicylic acid use is similar to that on benzoyl peroxide, other than the bleaching qualities.

Evidence to support the use of salicylic acid is limited, and current guidelines do not include it in management algorithms. Although salicylic acid has shown benefit, its place in therapy is variable. When added to other therapies, its efficacy is diminished; thus, it may be therapeutic in the beginning of treatment but not later on. Finally, salicylic acid is a safe option in pregnant patients with mild to moderate forms of acne (Pugashetti 2013).

Other OTC Products

Additional OTC agents that may be considered include those that contain sulfur, which has mild antibacterial and keratolytic properties. Often, it is found in combination with sodium sulfacetamide in order to hide sulfur's distinctive odor (Del Rosso 2009) or in combination with salicylic acid as a topical cleanser. Resorcinol also has mild antibacterial properties and is found either as monotherapy or in combination with sulfur. Use of these products is limited by a lack of supporting evidence.

PRESCRIPTION DRUG THERAPY OPTIONS FOR ACNE

Topical Retinoids

Topical retinoids prevent and reduce comedones by penetrating the follicles; they also have anti-inflammatory properties. These vitamin A derivatives target the retinoic acid receptors (RARs) and retinoid X receptors (RXRs), binding to them to implement their effects. Receptor subtypes include alpha, beta, and gamma, with RAR-γ and RXR-α being the most common types found in the skin. Topical retinoids effectively reduce and prevent microcomedone formation by altering cell differentiation of the skin. Their multipronged mechanism of action makes them an effective option in both noninflammatory and inflammatory acne.

The three TRs, tretinoin, tazarotene, and adapalene, are all available in various formulations (Table 1-3). Adapalene is the most receptor-specific, targeting RAR-β and RAR-γ, in treating underlying AV pathology. At least one study endorses adapalene as the preferred TR (Nast 2012). Because of their ability to open up the pores for penetration, TRs can be added to oral or topical antibiotics to provide synergistic comedolytic and anti-inflammatory effects and reduce the duration of antibiotic use (and thus antimicrobial resistance) (Thielitz 2008).

Dosing of TRs should start at the lowest concentration a few times a week and be titrated to nightly, as tolerated. Each TR is available in several concentrations and formulations. Clinical trials have shown the efficacy of each TR compared with placebos. Limited evidence suggests that tazarotene 0.1% is more effective than adapalene 0.1% and better than tretinoin 0.025%.

As a class, TRs have similar adverse effects. In comparative studies, tazarotene produces more irritation than adapalene or tretinoin. Tazarotene is FDA pregnancy category X; the others are labeled as category C. Adapalene is the least irritating of the TRs and the only one of the class that may be used concurrently with benzoyl peroxide (Thielitz 2008). Adapalene 0.1% was successfully used in the treatment of infantile acne in a small cohort study of 12 patients. Both comedonal and inflammatory lesions were resolved in 3–4 months with no significant adverse effects (Kose 2008).

Topical retinoids are limited by their adverse effects, which may result in nonadherence or discontinuation. The drying adverse effects are transient, and patients can expect to achieve tolerance in about 4–6 weeks. Patients should be counseled to manage these adverse effects with daily noncomedogenic moisturizers. The dosing or choice of vehicle may also be adjusted to encourage tolerance. For example, micronized gels and polymerized creams increase tolerability. In addition, sun exposure degrades TRs; thus, sunscreen should be applied during the day. Best results may be expected in about 3 months. Safety and tolerability evidence may prompt the clinician to prescribe adapalene first, but for the patient who cannot afford this more costly topical, other options should be considered.

Patients (or their parents, if children) should be educated to avoid spot treatment; the retinoid must be applied to the entire face for greatest effectiveness. Only adapalene should be used concurrently with benzoyl peroxide because the other TRs are unstable when mixed with benzoyl peroxide. Patients may then be advised to apply benzoyl peroxide in the morning and the TR at night.

Substantial evidence supports the use of TRs across all stages of acne severity as well as in maintenance therapy, as discussed in the following. They can be used as monotherapy or part of combination therapy, depending on the acne severity.

Topical Antibiotics

The two most-studied TABS used to treat AV are erythromycin and clindamycin; both are available as single agents or in fixed-dose combinations with other agents (see Table 1-3).

Table 1-3. Available Prescription Options to Treat Acne Vulgaris

Drugs	Available Formulations (Concentrations)	Dose	Common Adverse Effects	Place in Therapy
Topical Retinoids				
Adapalene	Cream (0.1%) Gel (0.1%, 0.3%) Lotion (0.1%)	Once daily (cream, gel: daily in the evening)	Dryness, erythema, photosensitivity, pruritus, scaling, stinging	Any stage
Tazarotene	Cream (0.05%, 0.1%) Foam (0.1%) Gel (0.05%, 0.1%)	Once daily in the evening		
Tretinoin	Cream (0.025%, 0.05%, 0.1%) Gel (0.01%, 0.025%) Micronized gel (0.04%, 0.08%, 0.1%)	Once daily in the evening		
Topical Antibiotics				
Clindamycin	Foam (1%) Gel (1%) Lotion (1%) Pledget (1%) Solution (1%)	Twice daily (foam: once daily)	Burning, dryness, erythema, oiliness, pruritus	Mild inflammatory acne; moderate to severe acne
Erythromycin	Gel (2%) Pad (2%) Solution (2%)	Twice daily (gel: once or twice daily)		
Topical Combinations				
Adapalene/BPO	Gel (0.1%/2.5%; 0.3%/2.5%)	Once daily	Burning, dryness, erythema, oiliness, pruritus	Any stage
Clindamycin/ tretinoin	Gel (1.2%/0.025%)	Once daily in the evening		
Clindamycin/BPO	Gel (1.2%/2.5%; 1.2%/5%)			
Erythromycin/BPO	Gel (3%/5%)	Once daily in the evening Twice daily		
Oral Antibiotics				
Doxycycline	Capsule (50–150 mg) Tablet (50–150 mg) Tablet (DR: 75 mg, 100 mg)	50–100 mg once or twice daily	GI upset, esophagitis, photosensitivity, tooth staining[a]	Moderate to severe acne
Erythromycin	Capsule (DR: 250 mg) Tablet (250–500 mg)	250–500 mg once or twice daily	GI upset, hepatotoxicity	
Minocycline	Tablet (ER: 45–135 mg)	1 mg/kg/day for 12 wk	Autoimmune disorders, dizziness, fatigue, headache, hepatotoxicity, hyperpigmentation, intracranial hypertension, vertigo[a]	
Tetracycline	Capsule (250 mg, 500 mg)	250–500 mg twice daily	GI upset, tooth staining[a]	
Trimethoprim/ sulfamethoxazole	Tablet (800 mg/160 mg)	800 mg/160 mg twice daily	Anemia, hypersensitivity reactions, rash	

Hormonal Therapy				
Combined oral contraceptives	Variable	Estrogen: Lowest dose possible Progestin: Variable Once daily	Breakthrough bleeding, breast tenderness, headache, nausea, weight gain	Any stage[b]
Spironolactone	Tablet (25 mg, 50 mg, 100 mg)	50–100 mg daily	Breast tenderness, hyperkalemia, hypotension, menstrual irregularities	Any stage
Other				
Azelaic acid	Cream (20%)	Twice daily	Hypopigmentation, pruritus, stinging	Mild to moderate acne
Dapsone	Gel (5%)	Twice daily	Erythema	Any stage
Oral isotretinoin	Capsule (10 mg, 20 mg, 30 mg, 40 mg)	0.5–1 mg/kg/day in two divided doses	Blood dyscrasias; hair, skin, and mucous membrane dryness; hepatotoxicity; hypertriglyceridemia; teratogenicity	Severe acne

[a]Should not be prescribed during pregnancy or in children 8 years or younger.

[b]Combined oral contraceptives can serve a dual purpose in patients who need contraception and have mild acne.

BPO = benzoyl peroxide; DR = delayed-release; ER = extended-release.

Information from: Del Rosso JQ, Kircik L, Gallagher CJ. Comparative efficacy and tolerability of dapsone 5% gel in adult versus adolescent females with acne vulgaris. J Clin Aesthet Dermatol 2015;8:31-7; Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics 2013;131(suppl 3):S163-86; Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol 2007; 56:651-63; and package inserts.

Topical antibiotics effectively reduce inflammation and *P. acnes.* A meta-analysis supported that topical clindamycin is effective at resolving inflammatory lesions; however, it also showed similar efficacy between benzoyl peroxide/salicylic acid and benzoyl peroxide/clindamycin. Furthermore, data analyses showed that benzoyl peroxide/clindamycin was only slightly better than benzoyl peroxide monotherapy, presumably because of increasing antimicrobial resistance (Seidler 2010).

Topical antibiotics are well tolerated, with an adverse effect profile similar to that of other topicals used to treat AV but less than that of TRs. Patients should be counseled about monitoring for these adverse effects and about proper use, similar to other topical agents.

In the pediatric population, TABs may be considered in mild inflammatory acne that is unresponsive to initial forms of treatment with a TR, benzoyl peroxide, or both. Otherwise, TABs are primarily used in moderate to severe forms of acne across all age groups. Because of growing antibiotic resistance, guidelines recommend against the use of TABs as monotherapy in any stage. Evidence also indicates that TABs, used in combination with TRs, are more effective and can be used for a shorter duration. To reduce the risk of resistance, it is suggested that these agents be used concurrently with benzoyl peroxide (Dreno 2015). Antimicrobial resistance, as a primary limitation, is further discussed later in the chapter.

Topical Azelaic Acid

The properties of topical azelaic acid affect all pathways of AV pathology, but its mechanism of action is not well defined. This agent acts as a comedolytic and antimicrobial against *P. acnes*. The package directions call for application twice daily to acne-affected areas. This agent has shown efficacy in clinical trials, but this is limited compared with other existing agents. Patients can expect to see benefit within 4 weeks.

A recent small study showed that azelaic acid 15% gel, which has FDA label approval for rosacea, was noninferior to adapalene 0.1% gel in both treatment and maintenance of mild to moderate inflammatory AV. Specifically, lesion count reduction and the Dermatology Life Quality Index questionnaire results were comparable between the treatment groups (Thielitz 2015). Studies of azelaic acid in combination with the TABs clindamycin or erythromycin showed greater efficacy in reducing total lesion counts and acne severity and

in increasing patient satisfaction than their respective monotherapies (Pazoki-Toroudi 2011, 2010).

The incidence of adverse effects with azelaic acid is low; skin irritation is the most significant effect. Darker-skinned patients should monitor for skin color changes and hypopigmentation. In the small study mentioned previously, adverse effects (e.g., dryness, scaling) were significantly less in the azelaic acid group than in the adapalene group.

Azelaic acid may be considered an option in mild to moderate inflammatory acne or mixed acne types. Evidence is insufficient to support its use as a primary form of therapy. The EDF guidelines provide a low strength of recommendation for use of azelaic acid in comedonal acne and a medium strength of recommendation for use in mild to moderate papulopustular acne. The AAP guidelines do not mention its use in AV management, and the AAD guidelines dictate that it is not as effective as TRs. However, azelaic acid is FDA pregnancy category B and therefore a safe alternative in pregnant patients. It also may be considered in long-term maintenance therapy because its adverse effect profile is more tolerable than that of TRs.

Topical Dapsone

Twice-daily dapsone was FDA approved in 2009 as a topical agent to treat AV. It is considered an antibiotic but acts as an inflammatory agent in acne management. In clinical trials, statistically significant reductions in both noninflammatory and inflammatory lesions were seen at both the 4- and the 12-week marks (Draelos 2007). A recent study compared use between women 18 years and older and female adolescents 12–17 years old for 12 weeks. Although statistically significant reductions occurred in noninflammatory and inflammatory lesions in both groups, clinical success was greater in the adult group, suggesting that topical dapsone is more effective in adults overall (Del Rosso 2015).

Because dapsone is a topical agent, the risk of hemolytic anemia or severe skin reactions is theoretically less than with its oral counterpart. However, postmarketing reports indicate cases of methemoglobinemia, which led to updates in the package insert in July 2015. Dapsone is otherwise well tolerated, with minimal adverse effects. If applied together with benzoyl peroxide, the skin can temporarily turn yellow or orange.

Given its limited amount of evidence as a newer medication, dapsone's place in therapy is still unclear. Data are insufficient to show its efficacy in the pediatric population, and only the AAP guidelines mention dapsone as a substitute for TABs; the other guidelines were published before dapsone was approved.

Oral Antimicrobials

Tetracycline, minocycline, doxycycline, erythromycin, and trimethoprim/sulfamethoxazole are common oral antibiotics (OABs) used to treat moderate to severe AV (see Table 1-3). Oral antibiotics reduce *P. acnes* and have anti-inflammatory effects. The second-generation tetracyclines minocycline and doxycycline have lipophilic properties, allowing penetration into infected follicles and directly reducing *P. acnes*. Patients can expect to see a treatment response within 6–8 weeks.

Dosing varies depending on the OAB used. The minocycline extended-release formulation is the only OAB that has FDA label approval for AV; it is dosed by weight at 1 mg/kg/day for 12 weeks. Tetracycline and erythromycin have the most data. However, the AAD and AAP guidelines both recommend using minocycline or doxycycline over tetracycline because of greater effectiveness. A Cochrane review of minocycline's role in therapy, however, showed that it was no better than other OABs for AV (Garner 2012). It can be inferred that antimicrobial resistance to minocycline is also increasing. In a meta-analysis comparing OABs with combined oral contraceptives (COCs) in women, OABs were more effective at reducing acne lesions after 3 months of use; however, OABs were no better after 6 months of use (Koo 2014). In a randomized controlled study, doxycycline in combination with adapalene/benzoyl peroxide gel was noninferior to oral isotretinoin in severe nodular acne (Tan 2014).

The primary limitation to using OABs is the antimicrobial resistance associated with their use. Strategies have been suggested to minimize resistance. One strategy is to limit use to no longer than 3–4 months (Dreno 2014). If treatment with an OAB is required subsequently, the same agent should be used again. Monotherapy should be avoided, even in topical form. When signs of acne resolution are visible, particularly the lack of new inflammatory lesions, the antibiotic should be tapered off.

Patients can expect to see a response to treatment within 6–8 weeks. To avoid esophagitis, patients should take tetracyclines with a full glass of water and stay upright for at least 30 minutes to 1 hour. Ideally, tetracyclines should be taken on an empty stomach because food decreases their absorption; they can be taken 1–2 hours before, or 4 hours after, interacting foods/medications (Table 1-4). To prevent serious interactions, patients and children's parents should inform pharmacists and primary care providers of the use of any other drugs or of dietary changes.

The adverse effect profile varies with OAB. Drugs in the tetracycline class must not be used in pregnant women or children younger than 8 years because of the risk of tooth discoloration. In addition, patients may have dose-dependent photosensitivity and should be counseled to use sunscreen or avoid exposure to sunlight. Minocycline users may have skin pigmentation changes, particularly around the mucous membranes and pre-existing acne scars. Acute vestibular issues have been reported, particularly with high dosages. Although rare, minocycline has also been associated with severe rashes. The incidence of these adverse skin effects is greater with high doses and with longer use. Doxycycline and minocycline can cause esophageal irritation, with the former also causing nausea, especially when taken on an empty stomach. Both erythromycin and tetracyclines can cause GI intolerance. Trimethoprim/sulfamethoxazole is associated with a risk of severe skin reactions such as toxic epidermal necrolysis.

Table 1-4. Significant Drug-Drug and Drug-Food Interactions Associated with OABs Used to Treat AV

OAB	Interacting Drug/Food	Expected Interaction
Erythromycin	Carbamazepine Warfarin	• Increased concentrations of interacting drugs
Tetracyclines (doxycycline, minocycline, tetracycline)	Aluminum Antacids Antiepileptics Barbiturates Bismuth subsalicylate Calcium Carbamazepine Dairy products Iron Magnesium Methoxyflurane Penicillin Phenytoin Vitamins Warfarin	• Antiepileptics and barbiturates decrease the effect of doxycycline • Metal ion–containing drugs/food decrease the effect of OABs • Methoxyflurane: Fatal renal toxicity • Penicillin effects decreased • Warfarin effects increased
Trimethoprim/ sulfamethoxazole	CYP2C9 inducers QTc-prolonging drugs Warfarin	• Decreased effect • Increased risk of QTc prolongation • Effects increased

OAB = oral antibiotic.

Information from: Package inserts; and Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics 2013;131(suppl 3):S163-86.

Monitoring of adverse effects is warranted with all OABs, especially with dose increases. Patients taking any tetracycline should be monitored for headaches and blurred vision. Patients taking minocycline should be monitored for any flu-like symptoms because they could be indicative of a serious adverse event. Patients should also be monitored for any hypersensitivity reactions.

Oral antibiotics are generally effective in moderate to severe cases of acne and should be combined with other agents (e.g., benzoyl peroxide, TRs) to achieve outcomes and reduce resistance. Current guidelines suggest initially using doxycycline or minocycline because of less resistance, with the latter being more effective. On the contrary, both tetracycline and erythromycin greatly contribute to growing antimicrobial resistance, and erythromycin should only be an alternative in patients who cannot use tetracycline. Finally, trimethoprim/sulfamethoxazole is only an alternative when neither the tetracyclines nor erythromycin can be tolerated.

Combined Oral Contraceptives

The COCs with FDA label approval for the treatment of AV are ethinyl estradiol–containing products with different progestin forms, including norgestimate, norethindrone, and drospirenone. Combined oral contraceptives reduce sebum production in women with acne by suppressing androgen production in the ovaries.

A Cochrane review determined that COCs effectively resolve both inflammatory and noninflammatory acne, noting reductions in both numbers of lesions and in severity in the placebo-controlled trials that used COCs for AV. However, comparative effectiveness among the various COCs, progestin types, and dosages remains unclear. Despite updating the review with six additional trials, the authors' conclusions remained the same – that evidence is still insufficient to determine comparative efficacy between the COCs and other forms of acne treatment (Arowojolu 2012). Thus, in general, the lowest dose of estrogen and latest generation of progesterone possible are recommended to reduce the risk of adverse effects while providing benefit. The meta-analysis discussed earlier comparing OABs with COCs showed that efficacy in reducing acne lesions was comparable at 6 months; COCs were more effective at reducing lesions at 6 months versus 3 months, but OABs showed no difference between 6 months and 3 months. This implies that COCs should be first-line treatment for women with noninflammatory or inflammatory acne (Koo 2014).

Common adverse effects include nausea and vomiting, especially at the beginning of therapy; weight gain; headache; and breakthrough bleeding. Acne may initially worsen before

any signs of improvement. The risk of venous thromboembolism (VTE) is lower with low doses of estrogen and is much greater in patients predisposed to VTE (e.g., tobacco users, those with a personal or family history of VTE). Finally, bone growth may be of concern in the pediatric population, though the level of evidence around this concern is moderate at best.

If COCs are being used for their contraceptive effects in addition to acne treatment, patients should be counseled about daily adherence and backup contraception in case of missed doses. Patients should be advised to avoid smoking because of increased risk of thromboembolism, especially in those at least 35 years old. Maximal benefits of COCs can be seen after 3–6 months of use.

According to AAD and AAP, COCs may be considered first line for women with premenstrual acne or for women having anovulatory cycles, as in those with polycystic ovarian syndrome. For adolescents, patients should have had menses for at least 1 year before COC use is considered in moderate or severe acne because COCs can negatively affect bone growth (Eichenfield 2013). However, the EDF guidelines give only a low strength of recommendation to use antiandrogenic agents in the setting of severe papulopustular/moderate nodular acne.

Spironolactone

Spironolactone, an androgen receptor antagonist often used for the treatment of cardiovascular diseases, is another hormonal treatment for AV management in girls and women. The agent suppresses androgenic activity on sebaceous glands, thereby reducing acne-associated sebum production. Dosing is 50–200 mg daily. Data are insufficient regarding its efficacy in the pediatric population, but limited studies have shown efficacy in women 18 years and older. Patients may expect to see results after 3–6 months of therapy; they should be counseled to monitor for adverse effects and to adhere to laboratory monitoring when clinically warranted.

Common adverse effects of spironolactone include diuresis, hypotension, irregular menstrual cycles, and breast tenderness. Potassium concentrations should be monitored periodically, though patients are more susceptible to hyperkalemia if they have preexisting cardiac or renal conditions or are taking concurrent drugs that also increase potassium. A recent retrospective study showed that regular potassium monitoring was not necessary in healthy women; the hyperkalemia rate was almost the same as the baseline rate (Plovanich 2015). A boxed warning for spironolactone indicates that the drug can cause tumors in rats, but this warning stems from studies that used up to 500 times the normal dose. A recent analysis of 2.3 million adult Danish female-spironolactone users showed no increased risk of breast, uterine, ovarian, or cervical cancers (Biggar 2013).

A Cochrane review found insufficient evidence to support the use of spironolactone in AV management (Brown 2009). If first-line treatments have failed, this agent may be considered. Spironolactone may also be considered in women with severe acne who cannot use isotretinoin or whose isotretinoin therapy has failed, as well as in those who have high androgen concentrations and/or premenstrual acne.

Oral Isotretinoin

Isotretinoin is a vitamin A analog that can target all aspects of acne pathology. The AAD position statement notes substantial evidence supports the effectiveness of oral isotretinoin in treating severe forms of acne. It is effective in resolving acne and improving quality of life (Cyrulnik 2012) and is better in reducing lesions than other agents such as OABs and topical combinations (Zouboulis 2015).

Taken with food, the typical dosage of oral isotretinoin is 0.5–1 mg/kg/day for about 20 weeks or a cumulative dose of 120 mg/kg. An initial dosage of 0.5 mg/kg/day given in two divided doses may minimize the risk of adverse events. The suggested cumulative dose over 20 weeks should be 120–150 mg because smaller or larger dosages can increase the risk of relapse and adverse effects, respectively. For severe papulopustular acne, the EDF guidelines recommend 0.3–0.5 mg/kg/day continued for at least 6 months; this recommendation is based on expert opinion rather than on available evidence, which was deemed conflicting and limited in determining the best dosage (Nast 2012). Lower doses (0.1–0.2 mg/kg/day) might lessen the incidence of adverse effects, but the duration of use would be prolonged. However, according to one study in a small cohort of patients, high-dose isotretinoin (1.3 mg/kg/day or greater) is safe and effective in resolving acne and in improving the quality of life (Cyrulnik 2012).

The isotretinoin package insert noted common adverse effects of dry mucous membranes, muscle pain, and headaches. Serum triglycerides and liver enzymes may increase with use. In addition, blood dyscrasias may rarely occur. Controversial evidence has grown around the rare adverse events related to isotretinoin such as inflammatory bowel disease (IBD), suicidal ideation, and suicide. However, although IBD and suicide/suicidal ideation cases have been reported after isotretinoin use, evidence is inconclusive to support direct cause-and-effect relationships. Teratogenic effects are many, including, but not limited to, spontaneous abortions and abnormalities of the face, cardiovascular system, and parathyroid glands.

Although a highly effective drug, isotretinoin use is limited by its teratogenicity; the need for regular pregnancy testing; and required laboratory monitoring, which patients may find cumbersome. However, patients may accept these procedures to improve the psychosocial effects of severe acne. Laboratory monitoring includes a lipid panel, liver function tests, and a CBS. Because of isotretinoin's teratogenic effects, prescribers, distributors, pharmacies, and patients of both sexes must be registered within the iPLEDGE system before using the agent. It is imperative that women have two negative tests for pregnancy before starting the drug, then be tested monthly throughout therapy, immediately after the last dose, and 1 month after therapy ends.

Patient Care Scenario

A 26-year-old woman presents with noninflammatory, comedonal acne. As a teenager, she used topical tretinoin gel 0.025% for moderate inflammatory acne, and the agent resolved her acne within 4–6 weeks. What is best to recommend as therapy to help control this patient's current acne?

ANSWER

It is common for patients to present with acne later in life if they have a history of it. The patient currently presents with a mild form of acne (comedonal and noninflammatory). A TR is the recommended agent to use as maintenance therapy, with the option of adding benzoyl peroxide for its antibacterial effects. The patient could use the same TR that she used in the past, especially given that it was highly effective and resolved her past acne. However, considering the lower severity of the current presentation and the adverse effects of TRs (e.g., dry skin, irritation), the patient could use a lower strength of tretinoin, available at 0.01%, instead. The EDF guidelines also suggest topical azelaic acid an alternative to TR.

1. **Thiboutot D, Gollnick HP, Bettoli V, et al; Global Alliance to Improve Outcomes in Acne. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne Group. J Am Acad Dermatol 2009;60(suppl 5):S1-50.**
2. **Nast A, Dréno B, Bettoli V, et al; European Dermatology Forum. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol 2012;26(suppl 1):1-29.**

Patients should be counseled about reporting any suicidal ideation or changes in mood. They should be advised to discontinue any drying agents, to use moisturizers around the mucous membranes, and to use sunscreen. They should also be educated about using two effective forms of contraception throughout therapy (e.g., both a COC and male condom) as delineated by the iPLEDGE program. Finally, patients should be advised against blood donation to avoid the risk of exposing a pregnant woman to the agent.

According to the AAD, isotretinoin is effective in severe nodular acne or other stages of disease severity where first-line treatments have failed. The EDF guidelines give the highest recommendation to using oral isotretinoin in both severe papulopustular/moderate nodular acne and severe nodular/conglobate acne. Although isotretinoin is not the initial choice in the pediatric population, AAP gives a strong recommendation for its use in severe, refractory acne in adolescents and a lower strength of recommendation for use in pre-adolescents and younger.

APPROACH TO TREATMENT

The approach to treating AV depends on its presentation and severity (see Table 1-1). Each agent should target the different factors of pathology that contribute to acne. One study suggests treating AV as a chronic disease, such that early, aggressive therapy leads to better outcomes (Thiboutot 2009). Maintenance therapy also may be necessary to maximize outcomes. In general, a stepwise approach is recommended. It is suggested that targeting several pathologic factors using combination therapies, when appropriate, will result in faster clearance of the disease (Gollnick 2015). As the severity of acne increases, combination therapy becomes preferable. A mild case of acne may require only one therapeutic option, whereas the most severe form may warrant three different agents, including topical and systemic medications. Finally, according to current guidelines, management algorithms differ between the pediatric and adult populations (Figure 1-4 and Figure 1-5) (Thiboutot 2009).

Initial Treatment

Initial treatment should always begin with the lowest effective dosing possible. Mild acne in the pediatric population is generally treated with topical monotherapy, which can consist of either benzoyl peroxide or a TR. An oral or topical antibiotic may also be added in patients of color because of their higher risk of scarring from AV; however, because these antibiotics work synergistically with benzoyl peroxide and TRs, the risk of scarring is reduced and the rate of acne clearance is faster (Eichenfield 2013). In adults, the guidelines suggest that TRs are the mainstays of therapy in all stages, either as monotherapy or as part of combination therapy. As severity worsens, adding more topical and/or oral therapies is warranted. The lowest effective dose should be initiated and titrated to response and tolerability.

Maintenance Treatment

Across guidelines, except in the treatment of pediatric patients, the consistent recommendation for maintenance therapy is the use of a TR, with or without benzoyl peroxide, depending on the severity. The AAP guidelines do not explicitly review maintenance therapy. However, consistent with the other guidelines, AAP stresses that oral or topical antibiotics should not be used as a form of maintenance therapy. Hormonal therapy may be considered an option for maintenance in female patients, particularly for cyclic acne. Finally, if patients were successfully treated in the past with specific regimens, then present with recurrent acne, the same treatments should be considered first.

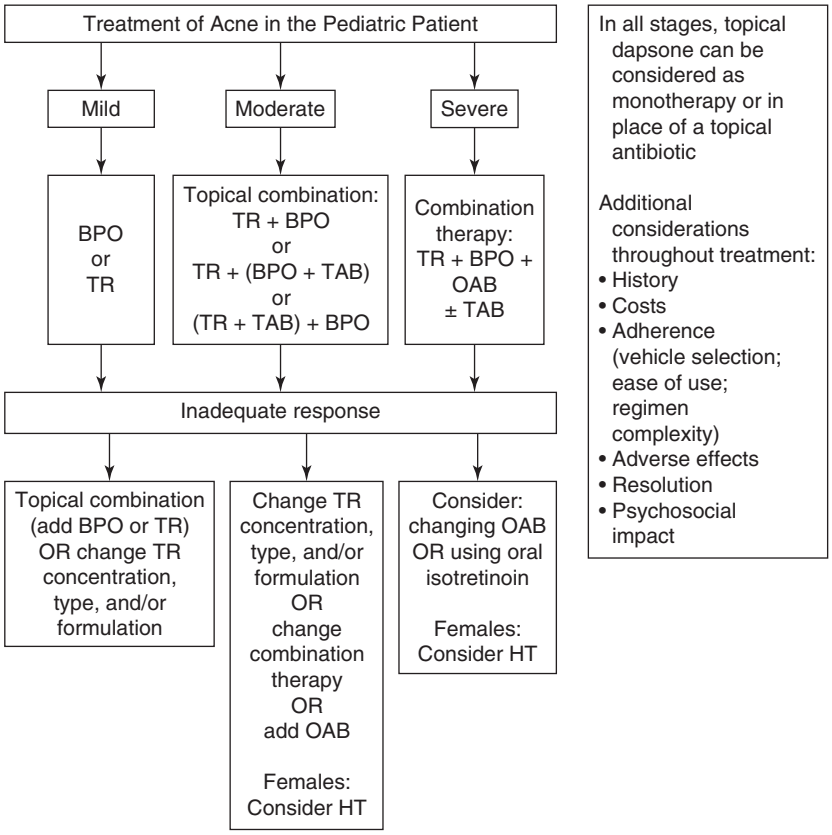

Figure 1-4. General approach to the treatment of acne according to severity in the pediatric patient.

BPO = benzoyl peroxide; HT = hormonal therapy; OAB = oral antibiotic; TAB = topical antibiotic; TR = topical retinoid.

Information from: Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics 2013;131(suppl 3):S163-86.

Monotherapy and Combination Regimens

The decision to use monotherapy or combination regimens depends on the severity of acne as well as patient preferences. In moderate to severe cases of acne, it may be more effective to use combination therapies than monotherapy.

Oral or topical antibiotics should never be used as monotherapy because of increasing rates of antimicrobial resistance. Several fixed-dose topical combination products are available; these may improve adherence and suppress resistance. When combining benzoyl peroxide and an antibiotic, the antibacterial effects are additive, allowing for reduced duration of antibiotic use and greater effectiveness. Several studies have shown the efficacy of fixed-dose combination therapies in pediatric patients. Substantial data analyses show the effectiveness of combining therapies to treat AV, particularly when including TR as one of the ingredients. The greatest limitation to fixed-dose combination products is the cost.

In a multicenter study, adapalene/benzoyl peroxide 0.1%/2.5% combination gel produced statistically significant improvement in patients with moderate facial acne compared with adapalene alone. Significant reductions occurred by the end of the first week of use. Safety profiles were comparable between groups (Gold 2009). In July 2015, a once-daily combination of adapalene and benzoyl peroxide 0.3%/2.5% received FDA label approval for the treatment of moderate to severe acne. In the phase III trial that provided evidence to support the approval, more than half of the group with severe acne experienced greater than 50% efficacy. Patients reported positive results as early as the first week of use. As with the individual agents, common adverse effects were mild to moderate, consisting of skin irritation, eczema, and a burning sensation. The main advantage to this fixed-dose combination product is its higher concentration of adapalene compared with that in the existing adapalene/benzoyl peroxide 0.1%/2.5% gel combination (Brooks 2015).

Counseling the Patient

Patients using any form of pharmacologic therapy should be counseled on when to expect benefits as well as on potential adverse effects, appropriate use, and duration of use. It may take up to 6–8 weeks before the patient receiving AV treatment begins to see therapeutic results. Furthermore, the skin may look worse before it looks better. Both common and

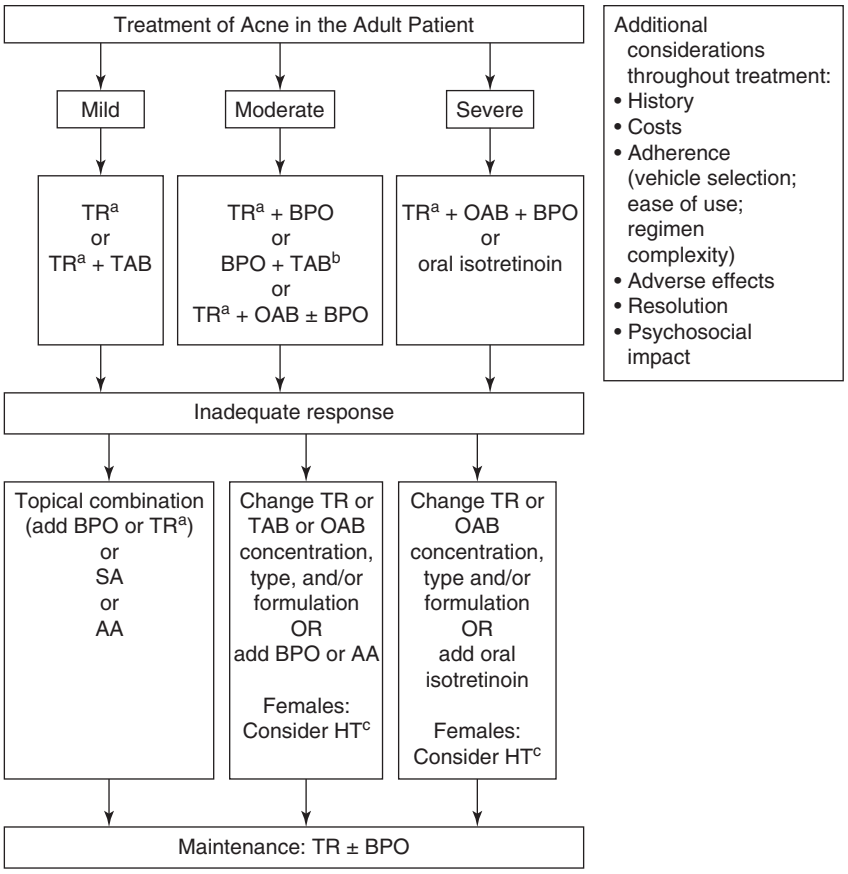

Figure 1-5. General approach to the management of acne in the adult patient according to severity. This algorithm accounts for guideline recommendations of highest strength of evidence, if applicable.

[a]EDF recommends adapalene as the TR of choice.

[b]EDF recommends fixed-combination topical BPO/clindamycin.

[c]This is considered combined oral contraceptives or antiandrogens such as spironolactone.

AA = azelaic acid; BPO = benzoyl peroxide; HT = hormonal therapy; OAB = oral antibiotic; SA = salicylic acid; TAB = topical antibiotic; TR = topical retinoid,

Information from: Nast A, Dréno B, Bettoli V, et al; European Dermatology Forum. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol 2012;26(suppl 1):1-29; Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol 2007;56:651-63; and Thiboutot D, Gollnick H, Bettoli V, et al; Global Alliance to Improve Outcomes in Acne. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne Group. J Am Acad Dermatol 2009;60(suppl 5):S1-50.

rare adverse effects, including allergic reactions, should be communicated to the patient. Adverse effects may be managed in several ways (e.g., changing formulations, frequency of use, dosing). Appropriate use will maximize the therapeutic benefits of any intervention. In addition, patients should be counseled on effective nonpharmacologic lifestyle management, if relevant, as discussed in the following.

Lifestyle Management

Because of the pathophysiology of AV, patients should limit or avoid any comedogenic cosmetics. Many of the pharmacotherapy options can cause dry skin; thus, a noncomedogenic moisturizer may need to be applied. Sunscreen of at least SPF 15 is recommended if sun exposure is anticipated. Patients should wash their faces twice daily with warm water and a mild cleanser (with or without benzoyl peroxide, as needed). Facial toners may be useful but can be drying if overused and may result in acne exacerbation. Patients should be counseled that harsher products or even harsher cleaning does not equate to improvement; rather, this can worsen the acne or even affect the tolerability of pharmacologic interventions (Eichenfield 2013). Any type of clothing or facial or headgear that is tightly worn can also trigger or exacerbate acne and should be avoided.

Evidence continues to be mixed regarding the role of dietary consumption and its effect on acne. However, if a patient determines that a specific food seems to worsen acne, it would be reasonable to advise the patient to discontinue the product. Some literature has shown a possible relationship between dairy products and acne in adolescents (Bowe 2010). Given that some studies show that diets high in glycemic load may contribute to acne in adolescents, this population could consider consuming diets consisting of lower glycemic load. However, the evidence does not support a strong recommendation about this association. Studies continue to investigate the roles of certain foods, such as chocolate, in AV pathology (Eichenfield 2013).

Role of the Pharmacist

The pharmacist is a critical health care provider in the management of AV. Pharmacists can identify drug-induced acne by thoroughly reviewing the patient's history and medications. Education on the appropriate use of pharmacotherapy (especially the application of topical agents) and on lifestyle modifications is necessary for successful outcomes. Pharmacists should counsel the patient on adverse effects and their management; the use of nonpharmacologic agents, if relevant; and expectations. Pharmacists are aptly positioned to discuss OTC choices of therapy. Because of the many available forms of OTC therapy, pharmacists can help individualize treatment according to the patient's needs, concerns, and goals of therapy.

Given that there are various vehicles of topical drugs, pharmacists can also guide the appropriate selection according to patient preferences and reported adverse effects. The drying effects of gel formulations are effective in patients with oily skin; some water-based gels can be helpful in patients with dry skin. Solutions containing alcohol can also cause irritation, so patients with sensitive or dry skin may benefit more from a cream- or lotion-based product.

Nonadherence rates, on average, are at least 50% among patients who are prescribed pharmacotherapy (Snyder 2014). Therefore, pharmacists are in the position to provide education and counseling. Adherence questionnaires such as the dermatologist-directed questionnaire can assist the pharmacist in identifying the level of adherence and the specific reasons for nonadherence (Pawin 2009; Thiboutot 2009). A systematic review reported that the most common risk factors behind nonadherence were adverse effects and young age (Snyder 2014). Thus, it would be reasonable to target education around the specific risk factors (Feldman 2011). Data from one study showed that 27% of patients do not pick up prescriptions for acne therapy, especially when prescribed more than one medication (Anderson 2015). Adherence tools such as web-based interventions or applications on smartphones may be helpful to improve adherence, particularly in the adolescent population (Bass 2015; Park 2014). The pharmacist may also explore the use of combination therapy or different vehicles of topical agents to help achieve patient-specific goals.

CONCLUSION

Whether it is selecting the appropriate therapy or providing effective counseling to maximize drug benefits, the ambulatory care pharmacist can play a vital role in assisting patients in treating their acne.

Topical retinoids continue to be the mainstay of treatment across all stages of acne, either as monotherapy or in combination with other products. Oral isotretinoin is an effective form of therapy in the context of severe acne. When using oral isotretinoin, patients should be enrolled in the iPLEDGE program because of the agent's teratogenic risks, and pharmacists should ensure that patients are using contraceptives.

Practice Points

Acne treatment options, when used appropriately, target different parts of acne pathogenesis. Therapy options include OTC products, topical agents, and oral medications. Choice of therapy should stem from an accurate diagnosis that accounts for the underlying pathology of the acne, disease severity, and patient preferences:

- **The various guidelines differ in their staging of acne severity, but the general approach to treatment is similar.**
- **Combination therapy is reasonable to target the multifactorial aspects of acne pathology.**
- **Benzoyl peroxide is a cost-effective option for patients with mild acne.**
- **Topical retinoids are effective agents in any type of acne and as maintenance therapy. Adapalene is the best tolerated and may be the first choice of therapy.**
- **When initial drugs do not resolve acne in female patients, oral hormonal therapies may be considered.**
- **Little evidence surrounds the use of spironolactone.**
- **Topical dapsone is an alternative for TABs in the pediatric patient.**
- **Oral isotretinoin should be considered in severe cases of acne. Pharmacists, pharmacies, and patients must register through the iPLEDGE system to reduce teratogenic risks in women using the medication.**
- **Maintenance therapy may consist of a TR, with the optional addition of benzoyl peroxide.**
- **Long-term use of oral and topical antibiotics should be avoided because of increasing microbial resistance. In addition, antibiotics as monotherapy should be avoided; a TR or benzoyl peroxide should be added to reduce the risk of resistance.**
- **In addition to pharmacologic agents, lifestyle management is equally important in the resolution of acne and prevention of scarring or future flares.**
- **Clinical pharmacists play a key role in counseling patients on the selected treatments for acne. Counseling points should include expectations, adverse effects, and lifestyle management.**

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Self-Assessment Questions

Questions 1–4 pertain to the following case.

T.F. is 20-year-old woman (weight 66 kg) who presents to her primary care provider with multiple comedones and a few inflammatory lesions on her face. She states that she has been stressed with her heavy college load and is even more stressed now because of how she looks. She reports that her last menses was about 2 months ago; on average has occurred every 2–3 months for the past year. T.F. has tried OTC benzoyl peroxide 10% for the past 3 months, but it has not helped. She would like a prescription to control her acne.

1. Which one of the following is the best initial choice of therapy for T.F.?

   A. Adapalene 0.1% daily
   B. Spironolactone 50 mg daily
   C. Ethinyl estradiol/drospirenone 20 mcg/3 mg
   D. Isotretinoin 30 mg twice daily

2. Two weeks after the agent of choice is initiated, T.F. returns to the office stating that her acne seems to be getting worse. Which one of the following is best to recommend for T.F.?

   A. Discontinue the agent and initiate another medication that is more potent.
   B. Increase the dose of the current medication.
   C. Add benzoyl peroxide 5% to the current agent.
   D. Continue the current agent.

3. Two months after her initial appointment, T.F. returns to the office. She reports that her acne has not resolved. On physical observation, you notice more inflammatory lesions and visible scarring on her face. You plan to initiate oral isotretinoin. Which one of the following is the most appropriate initial dosage for T.F.?

   A. 10 mg once daily
   B. 20 mg twice daily
   C. 40 mg twice daily
   D. 60 mg once daily

4. After completing the oral isotretinoin therapy, T.F. returns to the office and reports that she is doing much better and that the acne is almost cleared. However, she fears that the acne may reappear, even after successful treatment with the oral isotretinoin. Which one of the following is best to recommend as maintenance therapy for T.F.?

   A. Benzoyl peroxide
   B. Adapalene
   C. Topical dapsone
   D. Oral isotretinoin

5. A patient has begun using OTC benzoyl peroxide and believes that his acne is resolving. He has used it twice daily for about 3 weeks. He recently heard that the product causes severe allergic reactions and wonders if he should switch to a different agent. Which one of the following is the best counseling point to give this patient?

   A. Immediately switch to salicylic acid.
   B. Continue benzoyl peroxide.
   C. Continue benzoyl peroxide and take an antihistamine as prophylaxis.
   D. Use benzoyl peroxide less often.

6. An 18-year-old man presents with a diagnosis of moderate inflammatory acne. One year ago, he completed a 3-month course of clindamycin/benzoyl peroxide 1%/5% with complete resolution. Which one of the following treatment options for this patient would be best to reduce the risk of antimicrobial resistance?

   A. Doxycycline 100 mg daily
   B. Clindamycin 1% gel twice daily and doxycycline 100 mg daily
   C. Clindamycin/benzoyl peroxide 1%/5%
   D. Clindamycin 1% gel twice daily, doxycycline 100 mg daily, and benzoyl peroxide 10%

Questions 7 and 8 pertain to the following case.

T.J. is a 18-year-old woman who comes to the pharmacy to pick up tretinoin 0.025% cream. You notice the presence of some comedones mixed with a few papules scattered across her face.

7. According to your assessment, which one of the following best describes the severity of T.J.'s acne?

   A. Mild inflammatory acne
   B. Moderate acne
   C. Moderate to severe acne
   D. Severe acne

8. Which one of the following is best to recommend for T.J.?

   A. Use OTC benzoyl peroxide 5% along with the tretinoin 0.025%.
   B. Use OTC benzoyl peroxide 5% in the morning and tretinoin 0.025% at night.
   C. Ask the dermatologist to increase tretinoin 0.025% to tretinoin 0.05%.
   D. Ask the dermatologist to add erythromycin/benzoyl peroxide 3%/5%.

Questions 9 and 10 pertain to the following case.

A mother accompanies her son to the pharmacy seeking advice. T.Y., her 12-year-old son (weight 40 kg), has visible comedones, a marked number of inflammatory lesions, but no visible scarring or redness.

9. Which one of the following best describes the severity level of T.Y.'s acne?

   A. Mild acne
   B. Mild inflammatory acne
   C. Moderate acne
   D. Severe acne

10. According to your assessment of the severity, which one of the following is best to recommend as initial therapy for T.Y.?

   A. Benzoyl peroxide 2.5%
   B. Adapalene 0.1%
   C. Benzoyl peroxide/adapalene 2.5%/0.1%
   D. Benzoyl peroxide/adapalene 2.5%/0.1% and minocycline extended release 40 mg

11. An 11-year-old girl who has not yet had her menses receives a diagnosis of mild acne. Her mother does not want to purchase OTC products in light of the recent FDA warning about skin reactions. Which one of the following is best to recommend for this patient?

   A. Ethinyl estradiol 20 mcg/drospirenone 3 mg
   B. Dapsone 5%
   C. Clindamycin/tretinoin 1.2%/0.025%
   D. Adapalene 0.1%

12. A 14-year-old boy (weight 50 kg) with moderate acne is being initiated on minocycline extended release. Which one of the following is the best starting dose to recommend for this patient?

   A. 55 mg once daily
   B. 50 mg twice daily
   C. 105 mg once daily
   D. 100 mg twice daily

13. For the past 4 months, a 27-year-old woman has taken spironolactone 100 mg daily for moderate-severity acne. Her potassium concentration is 5.5 mEq/L. She reports that her acne has improved but that she still has some scattered facial lesions. She hates running to the bathroom often. Her menstrual cycles were irregular the first 3 months of use, but now seem to be regular again. Which one of the following is best to recommend for this patient?

   A. Continue spironolactone and reassess in another month.
   B. Reduce spironolactone dose to 50 mg and reassess in another month.
   C. Discontinue spironolactone and start benzoyl peroxide 5%.
   D. Continue spironolactone and start ethinyl estradiol 20 mcg/norethindrone 1 mg.

14. A 25-year-old woman presents with cyclic acne, which primarily appears the week before her menses. She has not tried to treat her acne with drugs. Which one of the following is best to recommend for this patient?

   A. Norethindrone 0.35 mg daily
   B. Ethinyl estradiol/norethindrone 20 mcg/1 mg daily
   C. Spironolactone 50 mg daily
   D. Adapalene 0.1% daily

15. A patient with a history of moderate acne was successfully treated with topical tazarotene 0.05% and benzoyl peroxide 5%. She is satisfied with the acne resolution, but the medication made her skin dry and irritated. Which one of the following is the best form of maintenance therapy to recommend for this patient?

   A. Benzoyl peroxide 5%
   B. Adapalene 0.1%
   C. Tazarotene 0.05%
   D. Tretinoin 0.01%

16. A 17-year-old female adolescent presents to the office with a severe form of acne. She has taken fluoxetine 20 mg daily for several months. She has a history of depression but denies suicidal ideation; her PHQ2 (Patient Health Questionnaire-2) is negative. The primary care provider would like to initiate oral isotretinoin but asks whether it is appropriate in this patient. Which one of the following is best to recommend for this patient?

   A. Initiate oral isotretinoin; monitor the patient for worsening depression.
   B. Initiate oral isotretinoin; no need to monitor for depression.
   C. Do not initiate oral isotretinoin; it can trigger suicidal ideation.
   D. Do not initiate oral isotretinoin until the patient discontinues fluoxetine.

17. You recommend benzoyl peroxide for a patient who presents with mild acne. He asks whether he should refrain from eating certain foods. Which one of the following is the best education point to include in this patient's treatment plan?

   A. Stay away from all types of food containing sugar.
   B. Refrain from consuming all dairy products.
   C. Avoid foods that trigger your acne development.
   D. Reduce intake of chocolate.

18. A patient was prescribed dapsone 5% gel for her acne and experienced a good response after 1 month. However, she still has some inflammatory lesions scattered across her face. The dermatologist heard about the update to the package insert regarding methemoglobinemia and asks whether he should prescribe refills. Which one of the following is the best answer to give the prescriber?

    A. The risk of this event occurring is low because it was not reported at the time of drug approval.
    B. There are case reports of methemoglobinemia associated with dapsone use, but it is more likely in patients with glucose-6-phosphate dehydrogenase deficiency.
    C. Patients using topical dapsone have no risk of methemoglobinemia compared to use of the oral form.
    D. Methemoglobinemia is a common adverse effect in patients using dapsone, but because she has had no problems with the drug, methemoglobinemia is unlikely to occur.

19. A 15-year-old girl presents with mild inflammatory acne that previously failed to respond to benzoyl peroxide. Now, her acne is failing to respond to topical tretinoin. Which one of the following is best to recommend for this patient?

    A. Switch tretinoin to adapalene.
    B. Start oral minocycline.
    C. Start topical clindamycin.
    D. Start topical combination clindamycin/benzoyl peroxide.

20. A mother presents to the pharmacy asking about OTC salicylic acid 2% cream to treat her 9-year-old daughter's occasional acne. The mother wonders whether it is effective; the daughter has sensitive skin and is afraid of trying anything for the acne. Which one of the following best supports the use of salicylic acid cream use in this patient?

    A. It is not as drying as benzoyl peroxide so it would be helpful for her sensitive skin.
    B. It does not have teratogenic effects.
    C. This low strength is best for her occasional acne.
    D. It is as effective as benzoyl peroxide in treating mild acne.

21. A 17-year-old male adolescent (weight 65 kg) is concerned about worsening acne corresponding to the start of high school football season. Previously, he had some acne scattered throughout his face, which he tried to resolve by using an OTC face wash as many as four times a day, with very little resolution. He now presents with more acne across his forehead, primarily composed of comedones, with few lesions. Which one of the following is best to initiate for this patient?

    A. Minocycline 65 mg once daily
    B. Dapsone 5% twice daily
    C. Salicylic acid 2% twice daily
    D. Tazarotene 0.05% once daily