

## **Therapeutic Overview Topical Acne Agents**

### **Overview/Summary**

Acne vulgaris, a disease of the pilosebaceous follicles, is the most common cutaneous dermatological disorder and primarily affects adolescents and young adults.<sup>1</sup> Acne manifests as open and/or closed comedones, as well as inflammatory lesions that may include papules, pustules or nodules. There are four pathogenic factors involved in the development of acne lesions, including follicular hyperkeratinization, increased sebum production, follicular colonization with *Propionibacterium acnes* and inflammation. The development of acne typically occurs during adolescence and resolves by the third decade of life; however, some individuals experience acne that persists into or first develops during adulthood.<sup>1,2</sup>

The initial evaluation and management of acne may be guided by rating the disease severity. There are several rating systems available for grading acne, most of which utilize lesion counting as well as a global assessment that takes into consideration the number, size and extent of the lesions. Although there is currently a lack of consensus on which rating system is best, it is recommended that clinicians be consistent.<sup>3</sup>

Topical therapy is currently considered first-line therapy, alone or in combination with other agents, for mild to moderate acne. Such agents include topical retinoids, topical benzoyl peroxide as monotherapy or in combination with erythromycin or clindamycin, other topical antibiotics, salicylic acid and azelaic acid. Other treatment options may include systemic antibiotics, estrogen-containing oral contraceptives and isotretinoin. For the treatment of moderate acne, systemic antibiotics may be added to the topical anti-acne regimen. Oral isotretinoin is typically reserved for the treatment of severe recalcitrant nodular acne and, due to its teratogenicity, is only available through the Food and Drug Administration's (FDA) iPLEDGE program.<sup>3</sup>

### **Medications**

**Table 1. Topical Acne Medications**

Generic Name (Trade name)	Medication Class	Generic Availability
<b>Single Entity Products</b>		
Adapalene (Differin <sup>®*</sup> )	Topical retinoids	✓
Azelaic acid (Azelex <sup>®</sup> )	Topical anti-bacterial	-
Benzoyl peroxide (Benzefoam <sup>®*</sup> , Benziq <sup>®*</sup> , Desquam-X <sup>®*</sup> , Lavoclen <sup>®*</sup> , Zaclir <sup>®*</sup> )	Topical anti-bacterial	✓
Clindamycin (Cleocin <sup>®</sup> T*, Clindagel <sup>®</sup> , Clindamax <sup>®*</sup> , Evoclin <sup>®*</sup> )	Topical anti-bacterial	✓
Dapsone (Aczone <sup>®</sup> )	Topical anti-bacterial	-
Erythromycin (Akne-Mycin <sup>®</sup> , Ery <sup>®*</sup> )	Topical anti-bacterial	✓
Sulfacetamide sodium (Klaron <sup>®*</sup> )	Topical anti-bacterial	✓
Tazarotene (Tazorac <sup>®*</sup> , Fabior <sup>®</sup> )	Topical retinoids	✓
Tretinoin (Atralin <sup>®</sup> , Avita <sup>®*</sup> , Retin-A <sup>®*</sup> , Retin-A Micro <sup>®*</sup> , Tretin-X <sup>®</sup> )	Topical retinoids	✓
<b>Combination Products</b>		
Adapalene/benzoyl peroxide (Epiduo <sup>®</sup> )	Topical anti-bacterial	-
Benzoyl peroxide/clindamycin (Acanya <sup>®</sup> , Benzacilin <sup>®*</sup> , Duac <sup>®*</sup> )	Topical anti-bacterial	✓
Benzoyl peroxide/erythromycin (Benzamycin <sup>®*</sup> , Benzamycin Pak <sup>®</sup> )	Topical anti-bacterial	✓
Benzoyl peroxide/salicylic acid/vitamin E (Inova <sup>®</sup> )	Topical anti-bacterial	-
Benzoyl peroxide/sulfur (Nuox <sup>®</sup> )	Topical anti-bacterial	-

Generic Name (Trade name)	Medication Class	Generic Availability
Benzoyl peroxide/urea (ZoDerm <sup>®*</sup> )	Topical anti-bacterial	✓
Benzoyl peroxide/vitamin E (Inova Kit <sup>®</sup> )	Topical anti-bacterial	-
Clindamycin/tretinoin (Veltin <sup>®</sup> , Ziana <sup>®</sup> )	Topical anti-bacterial/retinoid	-
Sulfacetamide sodium/sulfur (Avar <sup>®*</sup> , Clarifoam <sup>®*</sup> , Plexion <sup>®*</sup> , Rosanil <sup>®*</sup> , Sumaxin <sup>®*</sup> )	Topical anti-bacterial	✓

\*Generic available in at least one dosage form or strength.

## Clinical Guidelines

**Table 2. Clinical Guidelines**

Clinical Guidelines	Recommendations
American Academy of Pediatrics: <b>Evidence-based Recommendations for the Diagnosis and Treatment of Pediatric Acne (2013)<sup>3</sup></b>	<p><u>Mild acne</u></p> <ul style="list-style-type: none"> <li>Topical therapy alone or in combination is recommended as first-line treatment of mild acne.</li> <li>For patients of color in whom the propensity for scarring and postinflammatory hyperpigmentation is greater, initial treatment may also include an oral or topical antibiotic.</li> </ul> <p><u>Moderate acne</u></p> <ul style="list-style-type: none"> <li>Moderate acne may be treated with topical combinations, including a retinoid and benzoyl peroxide and/or antibiotics or with oral antibiotics in combination with a topical retinoid and benzoyl peroxide and/or topical antibiotics.</li> </ul> <p><u>Severe acne</u></p> <ul style="list-style-type: none"> <li>Severe acne should be managed with oral antibiotics and topical retinoids with benzoyl peroxide, with or without topical antibiotics.</li> <li>Hormonal therapy may be considered in pubertal females.</li> <li>Oral isotretinoin may also be considered for patients with severe acne.</li> </ul> <p><u>Over-the-counter treatment options</u></p> <ul style="list-style-type: none"> <li>Benzoyl peroxide is a safe and effective treatment option that may be used as monotherapy, in topical combination products for mild acne or in regimens of care for acne of all types and severities.</li> <li>When used with topical or systemic antibiotics, benzoyl peroxide may minimize the development of antibiotic-resistant <i>Propionibacterium acnes</i>.</li> </ul> <p><u>Topical retinoids</u></p> <ul style="list-style-type: none"> <li>Tolerability to topical retinoids may be improved by using noncomedogenic moisturizer that includes a sunscreen.</li> <li>Topical retinoids may be used as monotherapy or in combination with other anti-acne products for all types and severities of acne in children and adolescents of all ages.</li> </ul> <p><u>Topical antibiotics</u></p> <ul style="list-style-type: none"> <li>Topical benzoyl peroxide should be used in combination with prolonged topical or oral antibiotic therapy to reduce the emergence of resistant <i>Propionibacterium acnes</i>.</li> </ul> <p><u>Oral antibiotics</u></p>

Clinical Guidelines	Recommendations
	<ul style="list-style-type: none"> <li>• Treatment with oral antibiotics is appropriate for moderate to severe inflammatory acne vulgaris at any age.</li> <li>• Tetracycline derivatives (e.g., tetracycline, doxycycline, minocycline) should not be used in children younger than eight years of age.</li> </ul> <p><u>Oral isotretinoin</u></p> <ul style="list-style-type: none"> <li>• Isotretinoin is recommended for the treatment of severe, scarring and/or refractory acne in adolescents and may be used in younger patients.</li> <li>• Patients should receive extensive counseling regarding the avoidance of pregnancy and careful monitoring of potential side effects and toxicities.</li> </ul> <p><u>Topical fixed-dose combination therapies</u></p> <ul style="list-style-type: none"> <li>• Topical combination therapies may be useful for the treatment of all types and severities of acne.</li> </ul> <p><u>Hormonal therapy</u></p> <ul style="list-style-type: none"> <li>• Oral contraceptives may be useful as a second-line treatment option in pubertal females with moderate to severe acne.</li> <li>• Due to concerns regarding growth and bone density, it may be appropriate to withhold oral contraceptives for acne that is not associated with endocrinologic pathology until one year after onset of menstruation.</li> </ul>
<p>American Academy of Dermatology: <b>New Insights into the Management of Acne: An Update from the Global Alliance to Improve Outcomes in Acne Group (2009)<sup>2</sup></b></p>	<ul style="list-style-type: none"> <li>• Acne vulgaris should be managed early and aggressively as a chronic disease to limit scarring; the disease is self-limiting in 60% of cases.</li> <li>• Oral isotretinoin, the most effective acne vulgaris treatment developed to date, is administered during a 20 week period and sometimes must be given in repeated courses.</li> <li>• The combination of a topical retinoid and antimicrobial agent remains the preferred treatment approach for the majority of patients with acne vulgaris, especially in the presence of inflammatory lesions.</li> <li>• Due to the risk of bacterial resistance, antibiotics should be used for the shortest duration and should not be used as monotherapy but in combination with benzoyl peroxide.</li> <li>• Topical antibiotics combined with benzoyl peroxide and a topical retinoid may be used in mild to moderate acne vulgaris; oral antibiotics are recommended for moderate to moderately severe acne vulgaris.</li> <li>• Topical retinoids alone or in combination with benzoyl peroxide is recommended for the maintenance of acne vulgaris.</li> <li>• Long term antibiotic use may be required in the rare cases in which the patient experiences acne vulgaris flares when oral antibiotics are discontinued.</li> </ul> <p><u>Global alliance acne vulgaris treatment algorithm</u></p> <ul style="list-style-type: none"> <li>• For mild acne vulgaris (comedonal), treatment with a topical retinoid is considered first line; treatment with an alternative topical retinoid or azelaic acid or salicylic acid are considered alternatives.</li> <li>• For mild acne vulgaris (mixed and papular/pustular), treatment with a topical retinoid and a topical antimicrobial is considered first line; treatment with alternative topical retinoid and alternative topical antimicrobial, or azelaic acid are considered alternatives.</li> <li>• For moderate acne vulgaris (mixed and papular/pustular), treatment with oral antibiotic and a topical retinoid with or without benzoyl peroxide is considered first line; treatment with an alternative oral antibiotic and alternative topical retinoid with or without benzoyl peroxide are considered</li> </ul>

Clinical Guidelines	Recommendations
	<p>alternatives.</p> <ul style="list-style-type: none"> <li>For moderate acne vulgaris (nodular), treatment with an oral antibiotic and a topical retinoid and benzoyl peroxide is considered first line; treatment with oral isotretinoin or alternate oral antibiotic and an alternate topical retinoid (with or without) benzoyl peroxide/azelaic acid are considered alternatives.</li> <li>For severe acne (nodular/conglobate), treatment with oral isotretinoin is considered first line; treatment with high dose oral antibiotic and a topical retinoid and benzoyl peroxide are considered alternative.</li> <li>For maintenance therapy (mild to severe acne vulgaris), treatment with a topical retinoid with or without benzoyl peroxide is considered first line.</li> </ul>
<p>American Academy of Dermatology: <b>Guidelines of Care for Acne Vulgaris Management (2007)</b><sup>3</sup></p>	<p><u>Standard of care</u></p> <ul style="list-style-type: none"> <li>Topical therapy is the standard of care in acne vulgaris treatment.</li> <li>Benzoyl peroxide and combinations with erythromycin or clindamycin are effective treatments for acne vulgaris.</li> <li>Systemic antibiotics are a standard of care in moderate to severe acne vulgaris and treatment-resistant forms of inflammatory acne vulgaris.</li> <li>Intralesional corticosteroid injections are effective for large inflammatory lesions.</li> </ul> <p><u>Topical therapy</u></p> <ul style="list-style-type: none"> <li>Topical retinoids reduce obstruction within the follicle and are useful in the management of both comedonal and inflammatory acne vulgaris.</li> <li>The relative efficacy between topical retinoids (i.e., tretinoin, adapalene, tazarotene, isotretinoin [not available topically in the United States]) is unclear.</li> <li>Benzoyl peroxide is a bactericidal agent with the ability to prevent or eliminate the development of <i>Propionibacterium acnes</i> resistance, and is therefore used in combination with oral or topical antibiotics.</li> <li>Topical antibiotics (erythromycin and clindamycin) are effective in the treatment of acne vulgaris but are more effective when used in combination with benzoyl peroxide due to synergy as well as the resulting elimination or reduction of bacterial resistance.</li> <li>Salicylic acid has moderately effective and less potent comedolytic properties than topical retinoids and is therefore used in patients intolerant to dermatological effects caused by topical retinoids.</li> <li>Azelaic acid has shown to be effective, with comedolytic and antibacterial properties.</li> <li>The role of aluminum chloride, resorcinol, sodium sulfacetamide, sulfur and zinc in the management of acne vulgaris is unclear due to limited clinical evidence and/or peer-reviewed literature.</li> </ul> <p><u>Systemic antibiotics</u></p> <ul style="list-style-type: none"> <li>Doxycycline and minocycline are more effective than tetracycline.</li> <li>Minocycline has been shown to be superior to doxycycline in reducing <i>Propionibacterium acnes</i>.</li> <li>Erythromycin is effective but associated with bacterial resistance and therefore its use should be limited to those who cannot tolerate tetracyclines (i.e., pregnant women and children &lt;8 years old due to the potential damage to the skeleton or teeth).</li> </ul> <p><u>Hormonal agents</u></p> <ul style="list-style-type: none"> <li>Oral contraceptives containing norgestimate with ethinyl estradiol and</li> </ul>

Clinical Guidelines	Recommendations
	<p>norethindrone acetate with ethinyl estradiol are Food and Drug Administration approved for the management of acne vulgaris.</p> <p><u>Isotretinoin</u></p> <ul style="list-style-type: none"><li>• Isotretinoin, a vitamin A derivative, is approved for the treatment of severe recalcitrant nodular acne vulgaris and possibly effective in treatment-resistant acne vulgaris or acne vulgaris producing physical or psychological scarring.</li><li>• Since isotretinoin is a potent teratogenic, females of child-bearing age must only be treated if they are participating in the approved pregnancy prevention and management program (iPLEDGE).</li></ul>

**Conclusions**

According to Chapter 1200 of the Nevada Medicaid Services Manual section 1203.1A 3c, agents used for cosmetic purposes and hair growth are excluded from reimbursement. However, guidelines recommend treatment to reduce scarring, which is associated with moderate to severe acne. Moreover, acne is less common for older patients and is frequently a transient problem observed primarily in adolescent years.

**References**

1. Graber E. Treatment of acne vulgaris. UpToDate [database on the internet]. Waltham (MA): UpToDate; 2014 [cited 2014 May 28]. Available from: <http://www.uptodate.com>
2. Thiboutot D, Gollnick H, Bettoli V, Dreno B, Kang S, Leyden JJ et al. 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:S1-50.
3. Eichenfield LF, Krakowski AC, Piggott C, Del Rosso J, Baldwin H, Friedlander SF, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics. 2013;131:S163.
4. Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007 April;56(4):651-63.
5. Dals MV. Rosacea: pathogenesis, clinical features and diagnosis. UpToDate [database on the internet]. Waltham (MA): UpToDate; 2014 [cited 2014 May 27]. Available from: <http://www.utdol.com/utd/index.do>.