

# Therapeutic Options

## FOCUS ON ACNE VULGARIS

Acne vulgaris is a highly prevalent disease that affects the pilosebaceous units of the dermis.<sup>1</sup> It is characterized by comedones (open [blackheads] and closed [whiteheads]) and inflammatory lesions, including papules, pustules, and nodules.<sup>2,3</sup> Estimates suggest that up to 90% or more of teenagers suffer from some degree of acne, and that disease can persist into adulthood in as many as 50% of individuals.<sup>4,5</sup> Potential consequences of acne should not be underestimated. It may cause dysmorphia and permanent scarring, and may be associated with severe psychological and social impairment, with a risk of low self-esteem, anxiety, and depression.<sup>2,6</sup>

This article provides a focused review of drug therapy options for acne vulgaris, with a summary of recommendations from the most recently published guidelines<sup>5</sup> from the

Global Alliance to Improve Outcomes in Acne (“Global Alliance”).

### **PATHOGENESIS & CLASSIFICATION**

The pathogenesis of acne vulgaris is multifactorial and results from an interplay of several etiologic factors, including: (1) follicular hyperkeratinization and obstruction, (2) excess sebum production, (3) proliferation of *Propionibacterium acnes* within the hair follicle, and (4) an inflammatory immune response.<sup>4,6,7</sup> Genetic factors, stress, and certain dietary patterns (e.g., high glycemic load diets) may influence the development and severity of disease.<sup>4,7,8</sup>

Acne is usually classified according to its predominant morphology (comedonal [noninflammatory], papulopustular [inflammatory], nodular [inflammatory]) or by severity (e.g.,

mild, moderate, severe).<sup>1</sup> However, it is notable that there is no consensus on a single grading or classification system.<sup>9</sup> Generally speaking, mild acne refers to primarily comedonal disease with few papules and pustules; severity increases with the number of inflammatory lesions.<sup>3</sup> Severe disease typically refers to the presence of many large, painful nodules and pustules.<sup>3</sup>

### **TREATMENT**

Early, severity-appropriate treatment of acne is recommended to achieve the best possible patient outcomes and reduce chances of physical and psychological scarring.<sup>4,6</sup> The overall approach to therapy recommended by the Global Alliance is summarized in Table 1. Treatment is guided mainly by acne severity and the extent of disease, but disease duration, response

to previous therapies, predisposition to scarring, patient preference, and economics should also be considered.<sup>6</sup>

Effective agents target one or more of the key etiologic factors in acne pathogenesis<sup>3</sup> (see Table 2). Important practice points about the various therapeutic options are summarized in Box 1.

General care measures, such as avoiding acnegenic moisturizers and makeup, are appropriate for all patients. Gentle face washing with mild soap (or soapless cleanser) should be limited to no more than twice daily.<sup>10</sup> Rough scrubbing and frequent washing can cause follicular trauma, which can worsen the condition.<sup>3,10</sup>

Topical therapies are appropriate for most patients with mild to moderate acne.<sup>3</sup> As no single topical agent

addresses all of the etiologic factors implicated in acne pathogenesis, combination therapy is usually warranted. Since the microcomedo is the precursor of clinically apparent acne lesions, topical retinoids, which target the microcomedo via their anticomedogenic and comedolytic activity, are considered a foundation of therapy for almost all patients except those with the most severe disease.<sup>5,6</sup> Topical antimicrobials, including benzoyl peroxide and antibiotics, possess activity profiles complementary to the retinoids (see Table 2), and the combination of a topical retinoid with an antimicrobial agent is considered first-line therapy for the majority of patients.<sup>5,6</sup> The combination of a retinoid plus benzoyl peroxide targets three of the four pathophysiologic

factors and has not been shown to contribute to bacterial resistance.<sup>5</sup>

Systemic therapies are generally reserved for moderate to severe acne.<sup>3</sup> However, mild to moderate acne associated with scarring or significant psychosocial disability, or disease unresponsive to topical therapies, will require systemic therapy.<sup>6</sup> In most instances, systemic therapy should be combined with a topical agent effective against the microcomedo (e.g., a retinoid).<sup>6</sup>

Topical retinoids are recommended for maintenance therapy in most individuals with mild to moderately severe acne, with benzoyl peroxide added for antimicrobial effects when necessary.<sup>5</sup>

**Table 1 – Global Alliance acne treatment algorithm<sup>5,11,12</sup>**

Choice of Therapy	Acne Severity/Morphology				
	Mild	→	Moderate	→	Severe
	Comedonal	Mixed and papular/ pustular	Mixed and papular/ pustular	Nodular*	Nodular/ conglobate
First choice	Topical retinoid	Topical retinoid + Topical antimicrobial†	Oral antibiotic + Topical retinoid ± BPO	Oral antibiotic + Topical retinoid + BPO	Oral isotretinoin†
Alternatives <sup>§</sup>	Alt. topical retinoid or Azelaic acid   or Salicylic acid¶	Alt. topical antimicrobial† + Alt. topical retinoid or Azelaic acid	Alt. oral antibiotic + Alt. topical retinoid ± BPO	Oral isotretinoin or Alt. oral antibiotic + Alt. topical retinoid	High-dose oral antibiotic + Topical retinoid + BPO
Alternatives for females <sup>§</sup> **	See first choice	See first choice	Oral antiandrogen†† + Topical retinoid/ Azelaic acid   ± Topical antimicrobial†	Oral antiandrogen†† + Topical retinoid ± Oral antibiotic ± Alt. antimicrobial†	High-dose oral antiandrogen†† + Topical retinoid ± Alt. topical antimicrobial†

Alt. = alternate; BPO = benzoyl peroxide

\* With small nodules (<0.5 cm).

† Topical antimicrobials include benzoyl peroxide and antibiotics.<sup>5</sup>

‡ Use a second course in case of relapse.

§ Consider physical removal of comedones.

|| Azelaic acid is not approved in Canada for the treatment of acne vulgaris.

¶ Well-designed trials evaluating the safety and efficacy of salicylic acid are lacking.<sup>3</sup>

\*\* Options are limited for pregnant women.

†† Although the term “antiandrogen” is used in the Global Alliance treatment algorithm, alternate hormonal therapies that block ovarian and adrenal androgen production (e.g., combined oral contraceptives) may be useful for women who require medical therapy to control menstruation and/or those who desire contraception.<sup>12</sup>

**Table 2 – Impact of acne therapies on etiologic factors<sup>6</sup>**

Therapy	Sebum production	Hyperkeratinization	Inflammation	Reduction in <i>P. acnes</i>
<b>Topical therapies</b>				
Retinoids	–	++	+	–
Benzoyl peroxide	–	+	++	+++
Antibiotics	–	+	++	+++
<b>Systemic therapies</b>				
Antibiotics	–	+	+++	+++
Hormonal agents	++	++	Indirect	Indirect
Retinoids	+++	++	++	++

**Box 1 – Acne therapy practice points\***

**General**

- Topical therapies should be applied to the entire area affected by acne and not just active lesions, as seemingly unaffected skin is likely to have many evolving microcomedones.<sup>5,6</sup>
- Vehicle choice depends on skin type; creams are useful for dry or sensitive skin whereas gels and solutions may be more suitable for oily skin.<sup>4</sup> Lotions can be used on most skin types.<sup>4</sup>
- Most topical therapies require 6–8 weeks before noticeable improvement is seen.<sup>3</sup>

**Topical retinoids**

- Topical retinoids available in Canada include tretinoin, adapalene, and tazarotene.
- Erythema and scaling are common side effects; patients should be instructed to apply very small amounts initially.<sup>3</sup> Starting with the lowest available concentration of a product is a common approach to improve tolerability; gradual dosing has also been suggested (e.g., rinsing off after 3 hours for the first week, using twice weekly or every other day for the first few weeks).<sup>3,4,6,13</sup> Cream formulations may cause less irritation than gels.<sup>9</sup>
- Patients should be warned of a potential flare of inflammatory lesions upon starting treatment.<sup>6</sup>
- Adapalene 0.1% gel is as effective as, but less irritating than, tretinoin 0.025% gel.<sup>3</sup>
- Adapalene appears to be the best tolerated retinoid when used as part of a combination regimen.<sup>5</sup>
- Optimal response may not be evident until after 12 weeks of treatment.<sup>3</sup>

**Benzoyl peroxide**

- Available topical preparations range in strength from 2.5–10%.<sup>3</sup> Higher concentrations are more irritating, but not necessarily more effective.<sup>3,14</sup>
- If acne is very mild, benzoyl peroxide may be effective for initial therapy.<sup>13</sup>
- Response can be rapid, with a noticeable effect as early as 5 days.<sup>3</sup>
- Patients should be warned that fabrics (e.g., towels, bed sheets, clothing) that come into contact with benzoyl peroxide-treated skin may be bleached.<sup>3</sup>
- Irritant dermatitis, which often subsides as treatment continues, can be minimized by initiating treatment with a low-strength water-based product at a low application frequency (e.g., every 2 to 3 nights) and increasing to nightly or twice daily applications as tolerated.<sup>6,10</sup> Wash formulations, which are rinsed off after use, may decrease irritation and avoid bleaching.<sup>14</sup>

**Topical antibiotics**

- Topical antibiotics commonly used in Canada include clindamycin and erythromycin, and these agents appear to be similarly effective in mild to moderate acne.<sup>6</sup>
- Avoid antibiotic monotherapy; use with benzoyl peroxide (to limit antibiotic-resistant *P. acnes*) and a retinoid in mild to moderate acne.<sup>5</sup>
- Avoid concurrent use of topical and oral antibiotics, especially if chemically different.<sup>5</sup>
- Limit duration of use to short periods; assess response and continuing need at 6–12 weeks; discontinue when inflammatory lesions begin to resolve (usually within 4 months) or when improvement ceases or is only slight.<sup>5</sup>

**Combination products/therapies**

- Agents that are part of a combination regimen should be applied at separate times (e.g., benzoyl peroxide in the morning and a retinoid in the evening) unless they are known to be compatible.<sup>3,6</sup> Benzoyl peroxide has been shown to oxidize tretinoin if applied at the same time.<sup>3</sup>
- Fixed-dose topical combination products improve patient convenience, which may improve adherence; products containing a retinoid and benzoyl peroxide (as opposed to an antibiotic) as the antimicrobial may be the most desirable on a theoretical basis since they minimize the development of bacterial resistance.<sup>5</sup>
- To limit bacterial resistance associated with retinoid/antibiotic combinations, benzoyl peroxide should either be added or therapy should be changed to a retinoid ± benzoyl peroxide once inflammatory lesions have resolved.<sup>5</sup>

*Continued on page IV*

\* Dosing recommendations for most of the agents discussed are available in the review by Laubscher and colleagues<sup>10</sup> (see References, below, for URL) and in a related acne pharmacotherapy comparison chart from the RxFiles ([http://www.cfp.ca/content/suppl/2009/03/04/55.3.266.DC1/RxFiles\\_Acne\\_chart.pdf](http://www.cfp.ca/content/suppl/2009/03/04/55.3.266.DC1/RxFiles_Acne_chart.pdf)).

## Box 1 – Acne therapy practice points\* (continued)

### Oral antibiotics

- Tetracyclines are the oral antibiotics of choice.<sup>6</sup> Doxycycline has a better side effect profile than minocycline and is recommended as the first-line oral antibiotic.<sup>6,15</sup> Non-doxycycline tetracyclines are considered second-line agents, while erythromycin is generally a third-line agent (except in pregnant women and children <12 years of age).<sup>15</sup> The use of agents (e.g., trimethoprim ± sulfamethoxazole, azithromycin, cephalosporins, fluoroquinolones) that are commonly employed to treat systemic infections is discouraged.<sup>6</sup>
- Avoid antibiotic monotherapy.<sup>5</sup>
- Avoid concurrent use of oral and topical antibiotics, especially if chemically different.<sup>5</sup>
- Limit duration of use to short periods; assess response and continuing need at 6–12 weeks; discontinue when improvement ceases or improvement is only slight.<sup>5</sup> If additional antibiotic courses are used to treat relapses, the same antibiotic should be employed where possible.<sup>6</sup>
- Long-term oral antibiotics may be required as an alternative to oral isotretinoin in patients whose acne flares upon stopping oral antibiotics (despite continued use of topical retinoids).<sup>5</sup>

### Hormonal agents

- Hormonal agents are effective second-line agents for women with acne, regardless of whether or not androgen excess is present.<sup>3</sup> All available treatments share the common goal of opposing (directly or indirectly) the effects of androgens on the sebaceous gland (and, to a lesser extent, the follicular keratinocyte).<sup>6</sup> Hormonal therapies include androgen receptor blockers (e.g., cyproterone acetate, spironolactone, flutamide), low-dose glucocorticoids, and combined oral contraceptives.<sup>6</sup>
- Combined oral contraceptives have been shown to reduce inflammatory and noninflammatory acne lesions; the various formulations appear to be equally effective.<sup>3,16</sup> Contraceptives containing only a progestin may worsen acne.<sup>3</sup>
- Antiandrogen therapy often requires 3–6 months before significant improvement is seen.<sup>3</sup>

### Isotretinoin

- Isotretinoin is the most clinically effective anti-acne therapy available.<sup>6</sup> It affects all major pathogenic factors in acne development, and should be considered for all patients with moderate or severe recalcitrant acne.<sup>3,6</sup>
- 85% of patients who receive a dose of 0.5–1.0 mg/kg/day are virtually clear of acne by 16 weeks.<sup>6</sup>
- Concurrent use with topical agents is generally avoided as they worsen dryness that frequently occurs with isotretinoin.<sup>10</sup> Given that the drying effects of isotretinoin persist for several months after stopping therapy, delaying the initiation of topical retinoid maintenance treatment (where indicated) is often necessary.<sup>10</sup>
- Moderate to severe acne flares occur in ~6% of patients during the first few weeks of treatment; strategies employed in an attempt to reduce/control flares in individuals at highest risk (those with multiple macrocomedones and/or severe nodular acne) include initiating treatment at a lower dosage (0.25 mg/kg/day) and titrating upwards over 4–6 weeks, or overlapping treatment initiation with oral erythromycin for up to 2 months (concurrent use of isotretinoin with tetracyclines should be avoided as both can increase intracranial pressure).<sup>6</sup>
- Recommended laboratory monitoring for toxicity purposes includes serum lipids, complete blood count with differential, liver enzymes, and blood glucose levels; these tests should be done prior to initiating therapy and at monthly intervals during treatment.<sup>3</sup>
- In sexually active women of childbearing age, two reliable forms of contraception should be used during, and for 1 month after, isotretinoin treatment because of potential teratogenicity.<sup>3</sup>
- Depression and suicidal thoughts have been reported with treatment, although a causal relationship has not been shown.<sup>3</sup> Nonetheless, patients should be monitored for emotional changes and isotretinoin should be discontinued if significant depressive symptoms are identified.<sup>6</sup>

\* Dosing recommendations for most of the agents discussed are available in the review by Laubscher and colleagues<sup>10</sup> (see References, below, for URL) and in a related acne pharmacotherapy comparison chart from the RxFiles ([http://www.cfp.ca/content/suppl/2009/03/04/55.3.266.DC1/RxFiles\\_Acne\\_chart.pdf](http://www.cfp.ca/content/suppl/2009/03/04/55.3.266.DC1/RxFiles_Acne_chart.pdf)).

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