Management of acne

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Abstract

Precise classification methods are used to define acne according to type (comedonal, papulopustular, or nodular) and severity. The relative effectiveness of several topical and systemic agents has been established in clinical trials, making possible an algorithm of specific treatment decisions based on acne classification.

Key Points

■ Select medication based on the type and severity of a patient’s acne, as well as the patient’s skin type: creams, lotions, or ointments for dry skin; solutions or gels for oily skin.

■ Choose topical therapy whenever possible to minimize side effects.

■ Allow 6 to 8 weeks for most treatments to work before deciding to try another regimen or add other agents.

The surest route to success in treating acne vulgaris follows 3 steps. First, establish the type and severity of acne. Second, select medication appropriate for the patient’s condition and skin type. In general, patients with oily skin benefit from solutions or gels, while those with dry skin do better with creams, lotions, or ointments.1 Third, educate the patient about the disease, the different types of medications and their side effects, and expectations for improvement that are realistic. Realistic expectations should enhance compliance and lead to the successful resolution of a debilitating disease.

■ TYPES AND SEVERITY OF ACNE

There are 3 types of acne: comedonal, papulopustular, and nodular (Table 1), all of which result from a multifactorial pathophysiologic process in the pilosebaceous unit: (1) sebum production, (2) follicular hyperkeratinization, (3) proliferation and colonization by Propionibacterium acnes, and (4) the release of inflammatory mediators.2 The resulting lesions include noninflammatory open (blackheads) and closed (whiteheads) comedones, as well as inflammatory papules, pustules, and nodules.

Acne severity is rated according to the Combined Acne Severity Classification that classifies acne into mild, moderate, and severe, based on the number and type of lesions (Table 2).3 Determining acne type and severity serves as a guide to treatment (Table 3).
TREATMENT OPTIONS

A variety of medications are available for the treatment of acne vulgaris. Note that most treatment regimens should be used for at least 6 to 8 weeks to judge their effectiveness before considering alternative treatments or adding other agents. The Figure, an algorithmic guide to the treatment of acne, represents the author’s assessment of the current literature. Alternative approaches may be appropriate after discussing options with individual patients. Table 4 summarizes the strength of evidence for acne interventions and how each compares with other treatments for the same type of acne.

Topical agents

Salicylic acid, found in a number of over-the-counter cleansers, has both anti-inflammatory and mild comedolytic effects. It can be used as initial therapy for mild acne or as an adjunctive agent in a broader therapeutic regimen. In a placebo-controlled study of 114 patients, 2% salicylic acid lotion demonstrated a statistically significant improvement from baseline at 12 weeks (SOR: B).4 No side effect data were provided.

Tea tree oil comes from the Australian tree Melaleuca alternifolia and has had success anecdotally in treating various skin conditions. In a single-blind trial of 124 patients, 5% tea tree oil gel was compared with 5% benzoyl peroxide lotion in the treatment of mild-to-moderate acne. Both agents significantly reduced the number of inflammatory lesions and comedones (SOR: B).5 However, benzoyl peroxide was statistically superior to tea tree oil in reducing inflammatory lesions and had a faster onset of action. Encouragingly, patients treated with tea tree oil experienced fewer side effects.

Benzoyl peroxide (BPO) is a potent bactericidal agent with mild keratolytic properties. Several trials have shown the 5% concentration to be consistently superior to placebo at a statistically significant level in the treatment of mild-to-moderate acne, with a 30% decrease in lesion counts (SOR: A).6,7 In addi-
tion, two small trials involving 153 patients with mild-to-moderate acne compared the efficacy of different concentrations of topical benzoyl peroxide (2.5% vs 5% and 2.5% vs 10%) used twice daily.8 These trials demonstrated no differences in efficacy among the various preparations based on lesion counts, and there was no dose-response effect (SOR: A). Erythema and scaling occurred with almost identical frequency with the 2.5% and 5% concentrations but more often with the 10% concentration. Thus, the 2.5% and 5% concentrations appear to be preferable based on the balance of risks and benefits.

**Topical tretinoin** (Renova, Retin-A, Avita) is a comedolytic agent effective as monotherapy for non-inflammatory acne. In two randomized controlled trials involving 292 patients of comparable age, use of 0.02% and 0.05% tretinoin strengths showed a statistically significant reduction in comedones and papules with a dose-response effect after at least 4 to 8 weeks of treatment when compared with placebo (SOR: A).9,10 However, there was also a statistically significant increase in erythema and peeling that was maximal after 1 to 3 weeks and decreasing thereafter. In addition, an exacerbation of inflammatory lesions (pustular flare) may occur within 2 to 4 weeks of onset of therapy.11

**Adapalene** (Differin) is a synthetic naphthoic acid derivative with retinoid activity. Several large, randomized studies have shown that adapalene gel 0.1% and tretinoin concentrations ranging from 0.025% to 0.1% were comparable in reducing total lesion counts by 50% in 4 to 12 weeks (SOR: A).12-14 One trial found that adapalene 0.1% produced a statistically significant reduction greater than that with tretinoin 0.025% in both noninflammatory and inflammatory lesions at 12 weeks (SOR: A).12 Adapalene was also significantly better tolerated than tretinoin, as evidenced by less erythema, scaling, and dryness.12,15 Thus far, there have been no significant studies comparing adapalene to other topical agents such as benzoyl peroxide.

**Azelaic acid** (Azelex) is a dicarboxylic acid that possesses bacteriostatic properties and is structurally unrelated to any of the conventional acne therapies. In a single-blind trial of 309 patients comparing 20% AZA with 5% benzoyl peroxide and placebo, AZA yielded a significant decrease in papulo-pustular lesion counts by 35% compared with placebo. There was equivalent efficacy between AZA and benzoyl peroxide (SOR: B).16 Patients tolerated AZA better than benzoyl peroxide, with 9% of AZA recipients reporting a burning sensation that subsided after 2 weeks, and 15% of the benzoyl peroxide group reporting local side effects. In another controlled comparison, 20% AZA cream used twice daily for 5 to 6 months was comparable in efficacy to 0.05% tretinoin cream for patients with comedonal acne but statistically more effective in reducing the number of papules (SOR: B).17 Tretinoin caused significantly more erythema and scaling than did AZA.

**Tazarotene** (Tazorac) is the first of a family of receptor-selective acetylenic retinoids. In a multicenter, randomized controlled trial including 334 patients, tazarotene 0.1% and 0.05%, applied once daily for mild-to-moderate acne significantly reduced noninflammatory acne and total lesion counts when compared with placebo at 4 to 8 weeks (SOR: B).18 The 0.1% gel also significantly reduced inflammatory lesions at 12 weeks. Adverse effects were dose related, ranging from 5% to 13% and included erythema and burning. There are no published trials comparing tazarotene with other retinoids or benzoyl peroxide.

### Combined acne severity classification

<table>
<thead>
<tr>
<th>Severity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild acne</td>
<td>Fewer than 20 comedones, or Fewer than 15 inflammatory lesions, or Total lesion count fewer than 30</td>
</tr>
<tr>
<td>Moderate acne</td>
<td>20–100 comedones, or 15–50 inflammatory lesions, or total lesion count 30–125</td>
</tr>
<tr>
<td>Severe acne</td>
<td>More than 5 nodules, or Total inflammatory count greater than 50, or Total lesion count greater than 125</td>
</tr>
</tbody>
</table>
peroxide. Tazarotene is 30% to 70% more expensive than comparable topical agents such as tretinoin, benzoyl peroxide, and antibiotics.

**Topical antibiotics**

Topical antibiotics are effective in the treatment of mild-to-moderate inflammatory acne by reducing the population of *P. acnes* in sebaceous follicles and by suppressing chemotaxis. Several large randomized controlled trials demonstrated that topical clindamycin 1% and topical erythromycin 2% applied twice daily were consistently superior to placebo in reducing the number of papules and pustules in patients with moderate-to-severe acne (SOR: A). Furthermore, in two double-blind, randomized trials involving 334 patients, a combination gel containing clindamycin 1% and benzoyl peroxide 5% proved superior to each component alone in reducing inflammatory lesions, and superior to the clindamycin-only gel in reducing noninflammatory lesions (SOR: B). Trial data on the combination gel containing erythromycin 3% and benzoyl peroxide 5% are of poor quality; thus the same conclusion cannot be made.

**Oral antibiotics**

Oral antibiotics are most often used for moderate-to-severe inflammatory acne. They work by suppressing *P. acnes* growth, thereby reducing the production of inflammatory mediators. However, as systemic

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**TABLE 3**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Non-inflammatory acne</th>
<th>Inflammatory acne</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Comedonal</td>
<td>Papulo-pustular</td>
</tr>
<tr>
<td>Tretinoin (Renova et al)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Benzoyl Peroxide</td>
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<td>X</td>
</tr>
<tr>
<td>Adapalene (Differin)</td>
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<td>X</td>
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<tr>
<td>Antibiotics</td>
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<td>X</td>
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<tr>
<td>Azelaic acid (Azelex)</td>
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<td>X</td>
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<tr>
<td>Tazarotene (Tazorac)</td>
<td>X</td>
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<tbody>
<tr>
<td></td>
<td>Comedonal</td>
<td>Papulo-pustular</td>
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<tr>
<td>Oral contraceptives</td>
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<td>X</td>
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<tr>
<td>Erythromycin</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Doxycycline</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Minocycline</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Isotretinoin (Accutane)</td>
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<td>X</td>
</tr>
</tbody>
</table>

Adapted from Use of Systemic Agents in the Treatment of Acne Vulgaris, Am Fam Physician 2000;62.
Treatment of acne according to type and severity

**Mild comedones**
- Prescribe tretinoin or adapalene. Improvement after 6-8 wks?
  - Yes
  - Add benzoyl peroxide or topical antibiotic
  - Is improvement seen after 2-3 months?
    - Yes
    - Refer to dermatologist
    - No
    - Continue treatment as needed
  - No

**Moderate comedones**
- Prescribe tretinoin and a topical antibiotic or adapalene and a topical antibiotic
- Is improvement seen after 2-3 months?
  - Yes
  - Refer to dermatologist
  - No
  - Continue treatment as needed

**Mild-to-moderate papules/pustules**
- Prescribe benzoyl peroxide and a topical antibiotic. Improvement after 6-8 weeks?
  - Yes
  - Add an oral antibiotic
    - 1st line: tetracycline or erythromycin
    - 2nd line: doxycycline
    - 3rd line: minocycline
  - Is improvement seen after 2-3 months?
    - Yes
    - Continue treatment as needed
    - No
  - No
  - Refer to dermatologist

**Severe papules/pustules or nodulocystic acne**
- Is there a history of oral antibiotic failure or scar formation?
  - Yes
  - Prescribe oral isotretinoin or refer to dermatologist
  - No

If patient is female:

Use oral contraceptives as adjunctive therapy to any treatments described above if patient desires contraception. [Note: There is only anecdotal evidence to suggest decreased oral contraceptive efficacy when combined with oral antibiotics typically used in the management of skin conditions.]
agents, they cause more significant and diverse side effects than do topical agents. Unfortunately there are no head-to-head trials comparing different oral antibiotics, or comparing oral and topical antibiotics.

**Erythromycin.** In a randomized study of 200 patients with moderate-to-severe acne, erythromycin, 1 g in 2 divided doses daily, significantly reduced the comedone, papule, and pustule count after 8 weeks (SOR: B). The side-effect rate was 8%, usually associated with gastrointestinal irritation. Studies have shown that *P. acnes* exhibits greater resistance to erythromycin than to tetracycline.

**Tetracycline/doxycycline/minocycline.** Tetracycline and its lipophilic derivatives, doxycycline and minocycline, are the most commonly prescribed oral agents for acne vulgaris. As a class, tetracyclines should not be prescribed for pregnant women or for those younger than 9 years of age, to avoid the risks of tooth discoloration and bone growth retardation in the fetus or child. Various double-blinded, randomized controlled trials involving patients with mild-to-moderate acne have shown that tetracycline confers a statistically significant improvement over placebo as early as 6 weeks (SOR: A). Adverse effects include gastrointestinal upset, vaginal yeast infection, and a theoretical decrease in the efficacy of oral contraceptives.

Doxycycline, 100mg/d, has been shown to significantly reduce inflammatory lesions in a crossover trial of 62 patients (SOR: B). Its adverse effect profile is similar to that of tetracycline, though it tends to cause more photosensitivity (4% vs 1%).

In a recent Cochrane review of 27 studies, minocycline was shown to be an effective treatment for acne, but no randomized controlled trial evidence was found to support the benefits of minocycline in acne resistant to other therapies (SOR: A). A recent study demonstrated that minocycline has a greater tendency than tetracycline or doxycycline to cause rare adverse side effects, including serum-sickness-like reactions, drug-induced lupus, and hypersensitivity reactions. These factors, in addition to the higher cost, suggest that minocycline should not be a first line antibiotic choice for treating acne.

**Oral contraceptives**

Oral contraceptives (OCs) reduce the severity of acne vulgaris by decreasing the amount of circulating androgens. In 1997, a triphasic combination OC containing ethinyl estradiol 0.035 mg and increasing doses of norgestimate (0.180 mg, 0.215 mg, and 0.250 mg) was approved by the FDA for the treatment of acne in women. This decision was based on the results of a randomized, double-blind trial involving 257 patients in which the triphasic contraceptive was compared with placebo over 6 months (SOR: A). The OC group showed statistically significant improvement greater than that of the placebo group in all types of acne lesions. It also reduced total lesion counts by more than 53% in female subjects at 26 weeks, compared with lesion reductions of about 27% in controls. The principal adverse effect noted in this study was nausea.

**Isotretinoin**

Isotretinoin (Accutane) is an oral retinoid labeled for use in patients with severe, refractory, nodulocystic acne. In a randomized, crossover trial that included 33 patients, isotretinoin significantly decreased the number of nodulocystic lesions by 95% when compared with placebo, with only rare side effects of cheilitis and dermatitis (SOR: B). However, other studies suggest that cheilitis is fairly common and its absence may imply noncompliance or malabsorption of the drug. In addition, the FDA issued a warning in 1998 regarding possible increased risks in depression, psychosis, suicidal thoughts, and suicide attempts, though no conclusive evidence has been found. The typical dosage of isotretinoin is 0.5 to 1 mg/kg daily in two divided doses, with a standard cumulative maximum dose of 120 to 150 mg/kg per treatment course.

In April 2002, Roche Laboratories released the System to Manage Accutane Related Teratogenicity
### Medication options for acne vulgaris

<table>
<thead>
<tr>
<th>Evidence Strength*</th>
<th>Medication</th>
<th>Cost per month**</th>
<th>Relative efficacy</th>
<th>Comparator</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comedonal, papulopustular, or nodulocystic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Norgestimate/ethinyl estradiol</td>
<td>$31.08</td>
<td>&gt;</td>
<td>Placebo</td>
<td>Decreases comedone and inflammatory lesion counts</td>
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<tr>
<td><strong>Comedonal or papulopustular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Adapalene (gel)</td>
<td>$34.47</td>
<td>=</td>
<td>Tretinoin</td>
<td>Adapalene has better side-effect profile</td>
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<tr>
<td>A</td>
<td>Benzoyl peroxide</td>
<td>$7.99–$16.19</td>
<td>&gt;</td>
<td>Placebo</td>
<td>Price depends on generic vs brand, not concentration</td>
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<tr>
<td>A</td>
<td>Clindamycin (gel)</td>
<td>$34.73</td>
<td>&gt;</td>
<td>Placebo</td>
<td>Topical</td>
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<tr>
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<td>Erythromycin (gel)</td>
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<td>&gt;</td>
<td>Placebo</td>
<td>Topical</td>
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<tr>
<td>A or B</td>
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<td>$23.91</td>
<td>&gt;</td>
<td>Placebo</td>
<td>Evidence strength A for noninflammatory and B for inflammatory</td>
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<td>B</td>
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<td>$44.40</td>
<td>&gt;</td>
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<td>Topical</td>
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<tr>
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<td>Benzoyl peroxide</td>
<td>Azelaic acid has better side-effect profile</td>
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<tr>
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<td>Erythromycin</td>
<td>Topical</td>
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<tr>
<td>B</td>
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<td>=</td>
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<tr>
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<td>Salicylic Acid</td>
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<tr>
<td>B</td>
<td>Tazarotene (.05%)</td>
<td>$64.75</td>
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<td>Placebo</td>
<td>Side effects similar to those of topical retinoids</td>
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<tr>
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<td>$68.74</td>
<td>&gt;</td>
<td>Placebo</td>
<td>Side effects similar to those of topical retinoids</td>
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<td><strong>Papulopustular or nodulocystic</strong></td>
<td></td>
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<tr>
<td>A</td>
<td>Tetracycline</td>
<td>$8.38</td>
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<td>Oral</td>
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<td>Placebo</td>
<td>Oral</td>
</tr>
<tr>
<td>B</td>
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<td>=</td>
<td>Tetracycline</td>
<td>Oral. Higher resistance levels of <em>P acnes</em> to erythromycin</td>
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<tr>
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<td>$21.90</td>
<td>&gt;</td>
<td>Placebo</td>
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<tr>
<td>B</td>
<td>Minocycline</td>
<td>$21.90</td>
<td>=</td>
<td>Tetracycline</td>
<td>Oral</td>
</tr>
</tbody>
</table>

**KEY:** > is more effective than; < is less effective than; = is equivalent to.

*Evidence Strength:
A = At least two trials of acceptable quality showing moderate to strong statistical evidence for clinically meaningful endpoint and effect.
B = Evidence is of modest strength, such as when only one trial addresses a comparison, there is significant heterogeneity, large differences are not statistically significant, or poor trial quality prevents accepting strong statistical evidence at face value.

**Cost:** Referenced from a major on-line retail pharmacy.
MANAGEMENT OF ACNE

Give any treatment option 6 to 8 weeks to work before deciding to try a new one.

(S.M.A.R.T) program, aimed at preventing pregnant women from receiving isotretinoin.42 Major malformations may occur in 25% to 30% of fetuses exposed to isotretinoin.43 Under this program, female patients must have both a screening and confirmation pregnancy test (urine or serum) prior to receiving a prescription for isotretinoin. In addition, patients must commit to using 2 forms of birth control for at least 1 month prior to initiation of therapy, during therapy, and 1 month after discontinuing isotretinoin. During monthly visits, a pregnancy test must be obtained and no more than a 30-day supply of isotretinoin may be prescribed. Finally, pharmacists will fill prescriptions only if an isotretinoin qualification sticker is affixed, obtained after signing and returning the S.M.A.R.T Letter of Understanding.

In addition to procedural safeguards, it is necessary to monitor lipid levels (hypertriglyceridemia and hypercholesterolemia) and liver enzymes at the start of therapy and at each monthly visit. If elevations occur in these measurements, dosage reduction or drug discontinuation should be considered. Given the intensity of monitoring that is required, some family physicians may wish to refer patients who require Accutane to a dermatologist.

REFERENCES
24. Leyden JJ, Shalita AR, Satthian GD, Sefton J. Erythromycin 2% gel in comparison with clindamycin


