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.

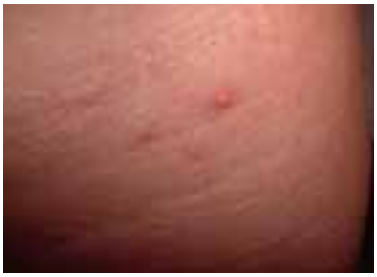
TYPES AND SEVERITY OF ACNE

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.

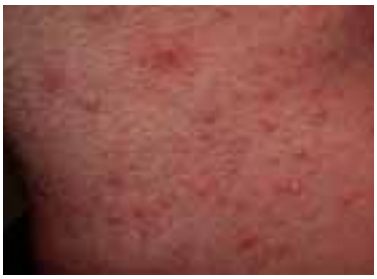
Acne severity is rated according to the Combined Acne Severity Classification that classifies acne into mild, moderate, and severe, based on the number and type of lesions (**Table 2**).[3] Determining acne type and severity serves as a guide to treatment (**Table 3**).

TABLE 1

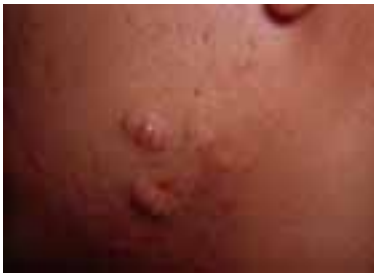
Types of acne



Comedonal (non-inflammatory)
Whitehead (closed): a dilated hair follicle filled with keratin, sebum, and bacteria, with an obstructed opening to the skin. *Blackhead (open):* a dilated hair follicle filled with keratin, sebum, and bacteria, with a wide opening to the skin capped with a blackened mass of skin debris.



Papulo-pustular (inflammatory)
Papule: small bump less than 5mm in diameter. *Pustule:* smaller bump with a visible central core of purulent material.



Nodular (inflammatory)
Nodule: bump greater than 5mm in diameter.

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 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 noninflammatory 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 ben-

TABLE 2

Combined acne severity classification

Severity	Definition
Mild acne	Fewer than 20 comedones, or Fewer than 15 inflammatory lesions, or Total lesion count fewer than 30
Moderate acne	20–100 comedones, or 15–50 inflammatory lesions, or total lesion count 30–125
Severe acne	More than 5 nodules, or Total inflammatory count greater than 50, or Total lesion count greater than 125

TABLE 3

Treatment options based on type of acne

Treatment	Non-inflammatory acne	Inflammatory acne	
	Comedonal	Papulo-pustular	Nodulocystic
Topical			
Tretinoin (Renova et al)	X	X	
Benzoyl Peroxide	X	X	
Adapalene (Differin)	X	X	
Antibiotics	X	X	
Azelaic acid (Azelex)	X	X	
Tazarotene (Tazorac)	X	X	
Systemic			
Oral contraceptives	X	X	X
Erythromycin		X	X
Tetracycline		X	X
Doxycycline		X	X
Minocycline		X	X
Isotretinoin (Accutane)			X

Adapted from Use of Systemic Agents in the Treatment of Acne Vulgaris, *Am Fam Physician* 2000;62.

zoyl peroxide. Tazarotene is 30% to 70% more expensive than comparable topical agents such as tretinoin, benzoyl peroxide, and antibiotics.

Topical antibiotics

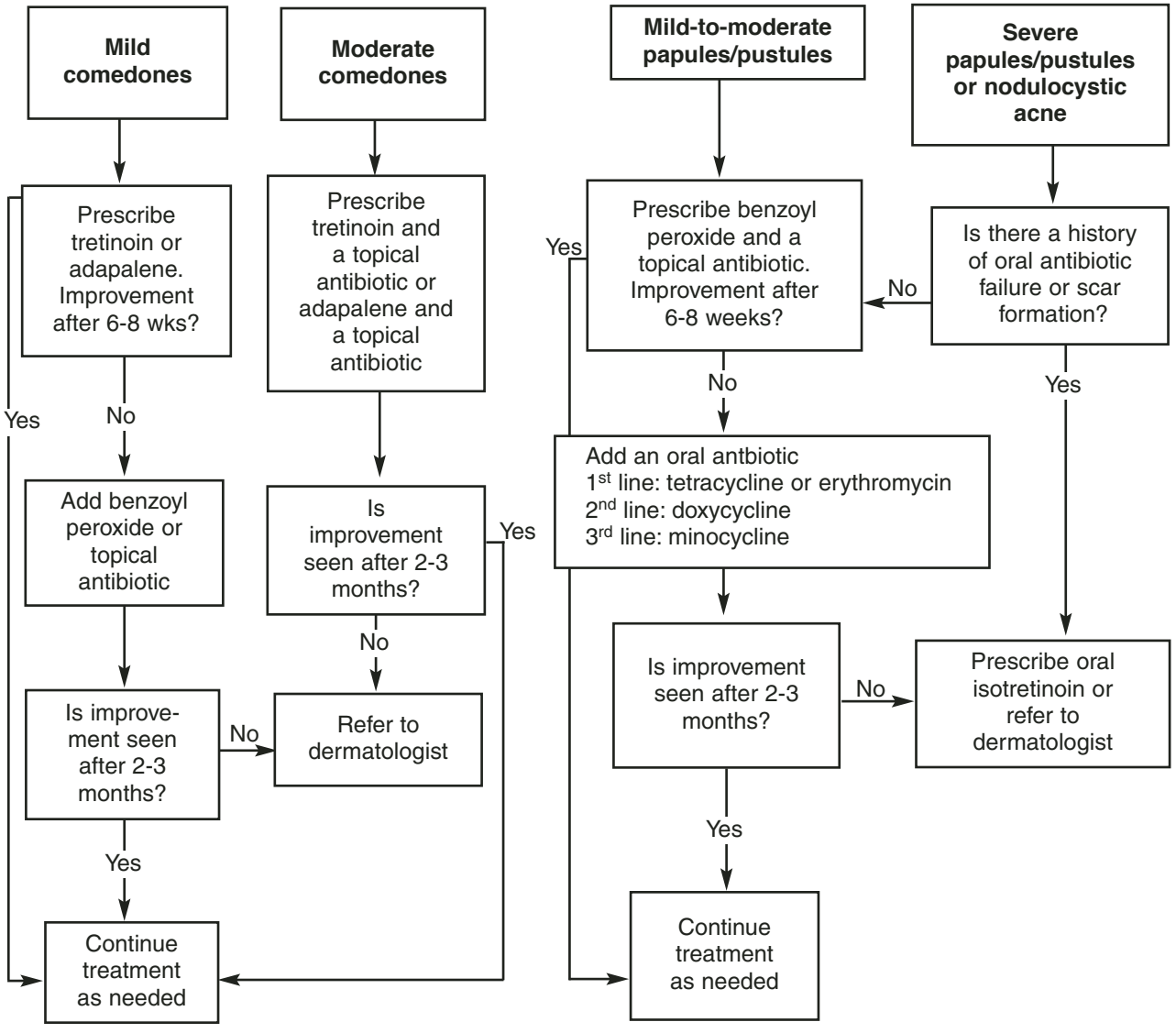
Topical antibiotics are effective in the treatment of mild-to-moderate inflammatory acne by reducing the population of *P acnes* in sebaceous follicles and by suppressing chemotaxis.[11] Several large randomized controlled trials demonstrated that topical clindamycin 1% and topical erythromycin 2% applied twice daily were consistently superior to placebo in reducing the number of papules and pustules in patients with moderate-to-severe acne (SOR: **A**).[19–23] Erythema and peeling were rare, comparable to that seen with placebo. Moreover, a randomized trial of 102 patients comparing 1% clindamycin with 2% erythromycin demonstrated that both medications significantly reduced the number of papules and comedones with no significant differences between the two (SOR: **B**).[24,25] 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**).[26] 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.[27] However, as systemic

FIGURE

Treatment of acne according to type and severity



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.][44]

P acnes has greater resistance to erythromycin than to tetracycline.

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**).[28] 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.[29]

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.[30] 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**).[31–33] 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**).[34] Its adverse effect profile is similar to that of tetracycline, though it tends to cause more photosensitivity (4% vs 1%).[35]

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**).[36] 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.[35] 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.[37] 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**).[38] 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**).[39] However, other studies suggest that cheilitis is fairly common and its absence may imply noncompliance or malabsorption of the drug.[40] 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.[40] 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.[41]

In April 2002, Roche Laboratories released the *System to Manage Accutane Related Teratogenicity*

TABLE 4

Medication options for acne vulgaris

Evidence Strength*	Medication	Cost per month**	Relative efficacy	Comparator	Comment
Comedonal, papulopustular, or nodulocystic					
A	Norgestimate/ ethinyl estradiol	$31.08	>	Placebo	Decreases comedone and inflammatory lesion counts
Comedonal or papulopustular					
A	Adapalene	$34.47 (gel)	=	Tretinoin	Adapalene has better side-effect profile
A	Benzoyl peroxide	$7.99–$16.19	>	Placebo	Price depends on generic vs brand, not concentration
A	Clindamycin	$34.73 (gel)	>	Placebo	Topical
A	Erythromycin	$18.31 (gel)	>	Placebo	Topical
A or B	Tretinoin	$23.91	>	Placebo	Evidence strength A for noninflammatory and B for inflammatory
B	Azelaic acid	$44.40	>	Placebo	Topical
B	Azelaic acid	$44.40	=	Benzoyl peroxide	Azelaic acid has better side-effect profile
B	Azelaic acid	$44.40	=	Tretinoin	Azelaic acid has better side-effect profile
B	Clindamycin	$34.73	=	Erythromycin	Topical
B	Clindamycin	$34.73	=	Benzoyl peroxide	Topical
B	Salicylic Acid		>	Placebo	Topical
B	Tazarotene	$64.75 (.05%) $68.74 (0.1%)	>	Placebo	Side effects similar to those of topical retinoids
B	Tretinoin	$23.91	>	Benzoyl peroxide	Tretinoin: stronger effect on comedones; BPO: stronger effect on papules
Papulopustular or nodulocystic					
A	Tetracycline	$8.38	>	Placebo	Oral
B	Doxycycline	$24.82	>	Placebo	Oral
B	Erythromycin	$27.15	=	Tetracycline	Oral. Higher resistance levels of *P acnes* to erythromycin
B	Minocycline	$21.90	>	Placebo	Oral
B	Minocycline	$21.90	=	Tetracycline	Oral

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.

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

1. Thiboutot DM. An overview of acne and its treatment. *Cutis* 1996; 57:8–12.
2. Leyden JJ. Therapy for acne vulgaris. *N Engl J Med* 1997; 336:1156–62.
3. Issued by funding/sponsoring agency: Management of Acne Volume 1: Evidence Report and Appendixes. Rockville, Md: Dept. of Health and Human Services (US), Public Health Service; 2001 Sep. Report No.: 01-E019. Issued by performing agency: Lehmann HP, Andrews JS, Robinson KA, Holloway VL, Goodman SN. Johns Hopkins Evidence-based Practice Center. Contract No.: 290–97–006. Sponsored by the Agency for Healthcare Research and Quality.
4. Eady EA, Burke BM, Pulling K., Cunliffe WJ. The benefit of 2% salicylic acid lotion in acne—A placebo-controlled study. *J Dermatol Treat* 1996; 7:93–6.
5. Basset OB, Pannowitz DL, Barnetson RS. A comparative study of tea-tree oil versus benzoyl peroxide in the treatment of acne. *Med J Aust* 1990; 153:455–8.
6. Hughes BR, Norris JF, Cunliffe WJ. A double-blind evaluation of topical isotretinoin 0.05%, benzoyl peroxide gel 5% and placebo in patients with acne. *Clin Exp Dermatol* 1992; 17:165–8.
7. Ede M. A double-blind, comparative study of benzoyl peroxide, benzoyl peroxide-chlorhydroxyquinoline, benzoyl peroxide-chlorhydroxyquinolone-hydrocortisone, and placebo lotions in acne. *Curr Ther Res Clin Exp* 1973; 15:624–9.
8. Mills OH Jr, Kligman AM, Pochi P, Comite H. Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. *Int J Dermatol* 1986; 25:664–7.
9. Pedace FJ, Stoughton R. Topical retinoic acid in acne vulgaris. *Br J Dermatol* 1971; 84:465–9.
10. Christiansen JV, Gadborg E, Ludvigsen K, et al. Topical tretinoin, vitamin A acid (Airol) in acne vulgaris. A controlled clinical trial. *Dermatologica* 1974; 148:82–9.
11. Berson DS, Shalita AR. The treatment of acne: the role of combination therapies. *J Am Acad Dermatol* 1995; 32:531–41.
12. Shalita A, Weiss JS, Chalker DK, et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. *J Am Acad Dermatol* 1996; 34:482–5.
13. Cunliffe W, Caputo R, Dreno B, et al. Clinical efficacy and safety comparison of adapalene gel and tretinoin gel in the treatment of acne vulgaris: Europe and U.S. multicenter trials. *J Am Acad Dermatol* 1997; 36:S126–34.
14. Galvin SA, Gilbert R, Baker M, et al. Comparative tolerance of adapalene 0.1% gel and six different tretinoin formulations. *Br J Dermatol* 1998; 139:S34–40.
15. Clucas A, Verschoore M, Sorba V, et al. Adapalene 0.1% gel is better tolerated than tretinoin 0.025% gel in acne patients. *J Am Acad Dermatol* 1997; 36:S116–8.
16. Cavicchini S, Caputo R. Long-term treatment of acne with 20% azelaic acid cream. *Acta Derm Venereol Suppl* 1989; 143:40–4.
17. Katsambas A, Graupe K, Stratigos J. Clinical studies of 20% azelaic cream in the treatment of acne vulgaris. Comparison with vehicle and topical tretinoin. *Acta Derm Venereol Suppl* 1989; 143:35–9.
18. Shalita AR, Chalker DK, Griffith RF, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double blind, vehicle-controlled study. *Cutis* 1999; 63:349–53.
19. Becker LE, Bergstresser PR, Whiting DA, et al. Topical clindamycin therapy for acne vulgaris. A cooperative clinical study. *Arch Dermatol* 1981; 117:482–5.
20. Ellis CN, Gammon WR, Stone DZ, Heezen-Wehner JL. A comparison of Cleocin T Solution, Cleocin T Gel, and placebo in the treatment of acne vulgaris. *Cutis* 1988; 42:245–7.
21. Pochi PE, Bagatell FK, Ellis CN, et al. Erythromycin 2 percent gel in the treatment of acne vulgaris. *Cutis* 1988; 41:132–6.
22. Lesher JL Jr, Chalker DK, Smith JG Jr, et al. An evaluation of a 2% erythromycin ointment in the topical therapy of acne vulgaris. *J Am Acad Dermatol* 1985; 12:526–31.
23. Dobson RL, Belknap BS. Topical erythromycin solution in acne. Results of a multiclinic trial. *J Am Acad Dermatol* 1980; 3:478–82.
24. Leyden JJ, Shalita AR, Saatjian GD, Sefton J. Erythromycin 2% gel in comparison with clindamycin

phosphate 1% solution in acne vulgaris. *J Am Acad Dermatol* 1987; 16:822–7.
25. Shalita AR, Smith EB, Bauer E. Topical erythromycin v clindamycin therapy for acne. A multicenter, double-blind comparison. *Arch Dermatol* 1984; 120:351–5.
26. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. *J Am Acad Dermatol* 1997; 37:590–5.
27. Sykes NL, Webster GF. Acne: a review of optimum treatment. *Drugs* 1994; 48:59–70.
28. Gammon WR, Meyer C, Lantis S, et al. Comparative efficacy of oral erythromycin versus oral tetracycline in the treatment of acne vulgaris. A double-blind study. *J Am Acad Dermatol* 1986; 14:183–6.
29. Eady EA, Jones CE, Tipper JL, et al. Antibiotic resistant Propionibacteria in acne: need for policies to modify antibiotic usage. *Br Med J* 1993; 306:555–6.
30. McEvoy GK, editor. *AHFS Drug Information.* Bethesda, Md: American Society of Health System Pharmacists; 1996.
31. Blaney DJ, Cook CH. Topical use of tetracycline in the treatment of acne: a double-blind study comparing topical and oral tetracycline therapy and placebo. *Arch Dermatol* 1976; 112:971–3.
32. Lane P, Williamson DM. Treatment of acne vulgaris with tetracycline hydrochloride: a double-blind trial with 51 patients. *Br Med J* 1969; 2:76–9.
33. Wong RC, Kang S, Heezen JL, et al. Oral ibuprofen and tetracycline for the treatment of acne vulgaris. *J Am Acad Dermatol* 1984; 11:1076–81.
34. Plewig G, Petrozzi JW, Berendes U. Double-blind study of doxycycline in acne vulgaris. *Arch Dermatol* 1970; 101:435–8.
35. Shapiro LE, Knowles SR, Shear NH. Comparative safety of tetracycline, minocycline, and doxycycline. *Arch Dermatol* 1997; 133:1224–30.
36. Garner SE, Eady EA, Popescu C, Newton J, Li Wan Po A. Minocycline for acne vulgaris: efficacy and safety (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2001.
37. Lucky AW. Hormonal correlates of acne and hirsutism. *Am J Med* 1995; 98:89S–94S.
38. Lucky AW, Henderson TA, Olson WH, et al. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. *J Am Acad Dermatol* 1997; 37:746–54.
39. Peck GL, Olsen TG, Butkus D, et al. Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. *J Am Acad Dermatol* 1982; 6:735–45.
40. Hanson N, Leachman S. Safety Issues in Isotretinoin Therapy. *Semin Cutan Med Surg* 2001; 20:166–83.
41. Layton AM, Knaggs H, Taylor J, Cunliffe WJ. Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment. *Br J Dermatol* 1993;129:292–6.
42. Accutane prescribing information. Nutley, N.J.: Roche Pharmaceuticals, 1998.
43. Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, et al. Retinoic acid embryopathy. *N Engl J Med* 1985; 313:837–41.
44. Helms SE, Bredle DL, Zajic J, et al. Oral contraceptive failure rates and oral antibiotics. *J Am Acad Dermatol* 1997; 36:705–10.