Am J Clin Dermatol 2012; 13 (3): 141-152
1175-0561/12/0003-0141/$49.95/0

American Journal of Clinical Dermatology
June 2012, Volume 13, Issue 3, pp 141–152

Topical Antimicrobial Treatment of Acne Vulgaris

An Evidence-Based Review

Ryan Gamble,[1] *Jeff Dunn*,[1] *Annelise Dawson*,[1] *Brian Petersen*,[1] *Lauren McLaughlin*,[2] *Alison Small*,[3] *Scott Kindle*[4] and *Robert P. Dellavalle*[1,5]

1 School of Medicine, University of Colorado, Aurora, CO, USA
2 College of Osteopathic Medicine, Rocky Vista University, Parker, CO, USA
3 College of Medicine, University of Arizona, Tucson, AZ, USA
4 College of Medicine, University of Nebraska, Omaha, NE, USA
5 Dermatology Service, Department of Veterans Affairs Medical Center, Denver, CO, USA

Contents

Abstract

Topical antimicrobial treatment is indicated for mild to moderate acne vulgaris. Our literature review includes searches of Ovid, MEDLINE, EMBASE, and the databases of the Cochrane Library. A detailed search strategy is included. All searches were limited to controlled trials and systematic reviews. No year limits were applied to the searches, but we focused on trials, guidelines, and reviews published since 2004, the year that the last review of topical antimicrobials was published in this journal. Several controlled trials demonstrate that benzoyl peroxide, topical antibiotics, and topical retinoids used in combination provide the greatest efficacy and safety profile for the treatment of mild to moderate acne, but there are few trials directly comparing different combinations of these topical therapies with one another. Additionally, robust studies comparing cost and efficacy of generic combinations of the above agents with proprietary fixed-dose combination therapies that may increase compliance are also lacking. Although they have not been extensively studied, alternative agents including dapsone, salicylic acid, azelaic acid, and zinc are safe and efficacious when combined with traditional therapies.

Acne vulgaris is a highly prevalent skin disease and the most common skin disorder in adolescents. Numerous treatment options are available, but topical antimicrobial therapy remains a mainstay for the management of mild to moderate acne because it offers localized treatment with less risk of systemic adverse effects.[1] We review recent trials evaluating topical antimicrobial therapy and assess current evidence relevant to the development of treatment suggestions and guidelines.[2]

1. Literature Search

The literature review conducted for this paper includes searches in the following databases: Ovid, MEDLINE, EMBASE, and the databases of the Cochrane Library, including the Cochrane Database of Systematic Reviews, Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Methodology Register, Technology Assessment Database, and Economic Evaluation Database.

Concepts searched included acne vulgaris and topical antibiotics. Terms that describe the concepts include 'acne vulgaris,' 'topical anti-microbial,' 'anti-infective agents,' 'anti-bacterial agents,' 'dermatologic agents,' 'benzoyl peroxide,' 'sodium sulfacetamide,' 'azelaic acid,' 'clindamycin,' and 'erythromycin.' These terms were searched both as text words and as subject headings.

All searches were limited to controlled trials and systematic reviews. No year limits were applied to the searches and they therefore extend as far back as the year range of each database up to April 2011 when they were conducted. Retrievals in Ovid MEDLINE go back to 1976, EMBASE to 1985, and the Cochrane Library to 1966. The Cochrane Library retrievals derive primarily from the CENTRAL database, supplemented by a handful from the DARE and the Economic Evaluation databases. For further details of the literature search strategy and citations retrieved, see Supplemental Digital Content 1, http://links.adisonline.com/DYZ/A3.

2. Mechanisms of Action of Anti-Acne Agents

Several factors contribute to development of acne including increased sebum production, abnormal keratinization with subsequent blockage of pilosebaceous ducts, microbial colonization most often by *Propionobacterium acnes*, and inflammation. Increased androgen levels at puberty result in greater sebum production contributing to the development of acne in this age group.[3]

Benzoyl peroxide acts through three primary mechanisms in the control of acne: it is bactericidal to *P. acnes* and also exhibits comedolytic as well as mild anti-inflammatory activity.[4-9] Benzoyl peroxide is lipophilic and concentrates inside sebaceous follicles to produce benzoic acid and reactive oxygen species. These products are thought to oxidize bacterial proteins thereby inhibiting protein and nucleotide synthesis, metabolic pathways, and mitochondrial activity.[9-11] Benzoyl peroxide does not appear to select for resistant *P. acnes* primarily due to its mechanism of action.[9-11] Antibiotics represent another primary drug category in the treatment of acne vulgaris. Erythromycin, a macrolide antibiotic, clindamycin, a lincosamide derivative, and tetracycline are the primary antibiotics utilized. All are bacteriostatic and interact with ribosomal subunits to inhibit protein synthesis.[12-14] These antibiotics inhibit synthesis of lipase, which is utilized by *P. acnes* for hydrolyzing serum triglycerides to glycerol (a bacterial growth substrate) and proinflammatory free fatty acids. Antibiotics also inhibit complement pathways and impair neutrophil chemotaxis.[15] Topical antibiotics are most effective in the treatment of inflammatory lesions but demonstrate mild activity against non-inflamed lesions and their use may contribute to the development of bacterial resistance.[16,17]

Retinoids are derivatives of vitamin A (retinol) that act by binding retinoic acid receptors and retinoic X receptors. Retinoids are desquamating agents that regulate differentiation and proliferation of keratinocytes and modulate keratinocyte adhesion molecules.[17,18] Retinoids also control inflammation by inhibiting neutrophil chemotaxis, toll receptor expression, and reactive oxygen species production on leukocytes.[18] Systemic retinoids also reduce sebum production, but topical retinoids do not.[16] The newer retinoids, adapalene and tazarotene, are receptor selective and may be more efficacious than older retinoid agents.[18,19] Adapalene is thought to be better tolerated than other drugs in the retinoid category.[19]

Antibiotics, retinoids, and benzoyl peroxide have complementary mechanisms of action that may contribute to their synergistic activity when used in combination.[17,20,21] In general, retinoids are more effective at reducing sebum production and keratinization, while antibiotics and benzoyl peroxide have greater effects at reducing inflammation and *P. acnes* counts.[17,20,21] The desquamating effect of retinoids also increases the penetration of antibiotics.[22,23] Interestingly, use of benzoyl peroxide with retinoids may decrease retinoid activity although newer retinoids such as adapalene are more stable and may be used in combination with benzoyl peroxide.[18,24]

3. Benzoyl Peroxide

Treatment of acne vulgaris with benzoyl peroxide alone or in combination with other topical treatments at concentrations of

2–5% is the standard of care for mild to moderate papular-pustular acne.[4,7-9,20,25,26] Use of benzoyl peroxide 2.5% appears to offer similar benefit to the 5% and 10% concentrations with fewer associated adverse effects.[9,27] Benzoyl peroxide monotherapy has been shown to have greater activity than topical tretinoin or isotretinoin against inflammatory lesions,[17,28,29] although two smaller trials demonstrated similar efficacy for both agents.[17,30,31]

Benzoyl peroxide is available in a variety of preparations including gels, washes, lotions, and creams. There is no clear superiority of these different preparations in terms of effectiveness.[4,32] Newer delivery systems to enhance efficacy and tolerability are also being investigated but have not been rigorously evaluated in comparison with current benzoyl peroxide formulations.[11,33-37]

4. Topical Antibiotics

Topical antibiotics are most effective for treating inflammatory acne, with limited efficacy against non-inflammatory lesions.[38] The most commonly available antibiotics for topical treatment of acne are erythromycin and clindamycin. Bacterial resistance is a persistent problem with antibiotics, especially when they are used as monotherapy.[39] The efficacy of erythromycin, in particular, may be declining due to bacterial resistance.[6,16,17] Increasing bacterial resistance has led many experts to recommend against the use of antibiotics as monotherapy. Nevertheless, topical antibiotics continue to play an important role in the treatment of acne in combination with other topical treatments including benzoyl peroxide, topical retinoids, or azelaic acid.

5. Benzoyl Peroxide and Antibiotic Combinations

The benefit of combining topical antibiotics with benzoyl peroxide over using either as monotherapy has been demonstrated in several trials.[25,40-43] Two large randomized, double-blind, controlled studies from 2008 showed that benzoyl peroxide 2.5% and clindamycin 1.2% gel significantly reduced lesion counts and demonstrated similar tolerability compared with clindamycin or benzoyl peroxide monotherapy.[43] A smaller study from 2009 found that a novel solubilized form of benzoyl peroxide 5% alone showed greater reduction of non-inflammatory lesions compared with combined benzoyl peroxide 5% and clindamycin 1%. Both groups showed comparable reduction of inflammatory lesions although benzoyl peroxide displayed more early adverse cutaneous effects than combination therapy[44] (see table I).

A recent meta-analysis determined that combination benzoyl peroxide 2.5% or 5% with clindamycin outperformed benzoyl peroxide and clindamycin monotherapy in treating inflammatory lesions and that reduction of non-inflammatory lesions with benzoyl peroxide 2.5% and clindamycin was significantly greater than any of the other treatments.[47] A study by another group[48] also showed that benzoyl peroxide 2.5% and clindamycin preparation demonstrated similar efficacy to benzoyl peroxide 5% and clindamycin preparation but was better tolerated.

A randomized controlled trial of patients with mild to moderate inflammatory acne with a 4-week washout prior to trial entry, showed that topical treatment regimens containing erythromycin and benzoyl peroxide outperformed oral tetracycline regimens for treating resistant acne with fewer systemic adverse effects.[46,49] Benzoyl peroxide monotherapy produced similar results to combined erythromycin and benzoyl peroxide treatment in both primary outcome measures, although it produced greater skin irritation than the erythromycin and benzoyl peroxide combination.[46,49]

6. Retinoid and Antibiotic Combinations

Topical retinoid and antibiotic combination therapies are also indicated for the treatment of patients with mild to moderate inflammatory acne. Several studies have demonstrated that combination therapy with topical retinoids and antibiotics produces significantly faster and greater clearance of acne than topical antibiotics or topical retinoids alone.[50-54] The combination of retinoids with antibiotics may be less irritating to the skin compared with monotherapy[52,53,55,56] although one group[50] noted that adapalene and clindamycin combination therapy was more irritating than either agent used alone.

Combining clindamycin with the newer topical retinoids adapalene and tazarotene is more efficacious than clindamycin and tretinoin combination therapy.[57] Adapalene also causes significantly less skin irritation than tretinoin when used in combination with topical clindamycin.[58] Unfortunately, these agents are also more costly. As with benzoyl peroxide and antibiotic preparations, topical retinoids and antibiotics combination therapy can be prescribed as separate products that are used together or fixed combination preparations that exist as a single product, the former being less expensive, with the latter being easier to use.

7. Other Topical Treatment Options

Additional options for topical treatment of acne include dapsone, zinc, sodium sulfacetamide, salicylic acid, azelaic acid, and allylamines. Topical dapsone 5%, alone or in combination

Table I. Trials of BPO and antibiotic combination therapy published since 2004

Study (no. of patients)	Design	Treatment	Results	Adverse effects
Kircik et al.[44] (n = 65)	Randomized, investigator-blind, multicenter 4 or 12 wk split-face study in patients aged 11–45 y with moderate acne	Twice daily for 4 or 12 wk: solubilized BPO 5% gel to one side of face; CL 1% and BPO 5% gel to contralateral side of the face	Solubilized BPO gel showed greater reduction in non-inflammatory lesion count than did CL and BPO at wk 1 and 2 ($p \leq 0.01$) as well as at wk 3, 4, and 12 ($p \leq 0.05$); comparable reductions in inflammatory lesion count at all timepoints	Well tolerated; less than mild dryness, erythema, peeling, stinging and burning and itching; significantly higher for solubilized BPO within the first 3 wk of treatment but comparable between both regimens by wk 4
Thiboutot et al.[43] (n = 2813)	Two, randomized, double-blind, controlled, multicenter, parallel, 12 wk studies in patients with moderate to severe acne	Once daily: CL 1.2% and BPO 2.5% gel; CL 1.2% gel; BPO 2.5% gel; vehicle control gel	The absolute and percentage reduction in inflammatory, non-inflammatory, and total lesion counts in the CL and BPO combination group was significantly higher than the other groups ($p < 0.001$)	Well tolerated; mild to moderate erythema, scaling, burning, itching, and stinging
Langner et al.[45] (n = 130)	Randomized, investigator-blind, multicenter, parallel-group 12 wk study of patients aged 12–39 y with mild to moderate acne	Once daily: CL 1% and BPO 5%; adapalene 0.1%	CL and BPO had an earlier onset of action and showed greater reductions in inflammatory lesions ($p \leq 0.001$) as well as total lesions ($p \leq 0.004$)	Well tolerated; mild dryness, erythema, scaling, burning, and pruritus; CL and BPO generally had fewer reports of adverse effects
Ozolins et al.[46] (n = 649)	Randomized, investigator-blind 18 wk trial in patients with mild to moderate acne	Oral oxytetracycline 500 mg twice daily plus topical placebo twice daily; minocycline 100 mg once daily plus topical placebo twice daily; topical BPO 5% twice daily plus oral placebo once daily; topical ERY 3% and BPO 5% combination twice daily plus oral placebo once daily; topical ERY 3% in the morning and BPO 5% at night plus oral placebo once daily	Topical BPO and topical ERY plus BPO were as effective as oral oxytetracycline and minocycline; BPO was the most cost-effective treatment; the topical regimens were most effective in treating resistant *Propionobacterium acnes*	Adverse systemic effects more likely to occur with oral antibiotics; local irritation more likely with topical treatments (especially BPO)

BPO = benzoyl peroxide; **CL** = clindamycin; **ERY** = erythromycin.

with adapalene 0.1% or benzoyl peroxide 4%, has been shown to be safe and efficacious, but may be more irritating to the skin than other topical agents[59-61] (see table II).

Topical antibiotics are also available in combination with zinc acetate. While zinc is ineffective as monotherapy,[4] a small, single-blind study of patients with mild to moderate acne treated with benzoyl peroxide 5% plus clindamycin 1% or erythromycin 4% plus zinc acetate 1.2% once daily found that, although both regimens improved total lesion count, clindamycin plus benzoyl peroxide had an earlier onset of action and showed significantly greater reductions of inflammatory lesions as well as total lesions.[64]

A small observational study demonstrated that 20% sodium sulfacetamide, when used in combination with a 50% sulfur foam, decreases acne, rosacea, and seborrheic dermatitis lesions without adverse effects.[65] Limited evidence also shows that salicylic acid alone,[4] or in combination with benzoyl peroxide[66] can improve acne. While limited safety data exist, it has been suggested as an alternative for patients who cannot tolerate topical retinoid therapy.[4] An Iranian trial of patients randomly assigned to combination azelaic acid 5% and clindamycin 2%, or either agent alone, showed that the combination gel significantly reduced total lesion count compared with baseline, as well as clindamycin 2% or azelaic acid 5% monotherapy.[62] The same group found similar results when combining azelaic acid with erythromycin and noted that the combination was more tolerable than either agent used alone.[63] Other studies have shown that azelaic acid at concentrations of 15–20% demon-

strates efficacy and tolerability comparable to tretinoin, benzoyl peroxide, and erythromycin monotherapy for the treatment of mild to moderate forms of acne.[67,68] Combination therapy utilizing benzoyl peroxide in combination with an allylamine (an antifungal agent), demonstrated more effective control of comedones than benzoyl peroxide monotherapy.[69]

8. Bacterial Resistance

The long-term, low-dose antibiotic regimens often prescribed for acne treatment have been associated with increasing *P. acnes* resistance.[17,70] Macrolides, such as erythromycin, are most associated with the development of bacterial resistance, although resistance to clindamycin, tetracycline, and other antibiotics is also quite high.[12,15-17,71,72] A study of *P. acnes* isolates in the UK found that resistance to erythromycin and clindamycin increased from nearly 35% in 1991 to over 55% in 2000.[73] A similar study comparing patterns of resistance in several European countries found that resistance to erythromycin and clindamycin may be as high as 90% in some regions.[74] *P. acnes* and *Staphylococcus epidermidis* strains can transfer resistance to *Staphylococcus aureus* and increase the lethality of that organism.[9] These findings have prompted scientists to recommend against the use of topical or oral antibiotics as monotherapy for acne vulgaris.[4,15,39,71,75,76] Data indicate that, since 2003, approximately 80% of prescriptions for topical antibiotics written by dermatologists are split evenly between clindamycin and combination clindamycin and benzoyl peroxide gel medications.[12,14]

Benzoyl peroxide appears to be effective in controlling both antibiotic-sensitive and antibiotic-resistant *P. acnes*.[9] Use of combined agents may allow for reduced dosages of antibiotics and lessen selection pressure for resistance.[9] Use of benzoyl peroxide may also help slow the spread of antibiotic-resistant *S. epidermidis* strains, which are associated with resistance in *S. aureus*.[9] One expert panel recommends that if antibiotics must be used for longer than 2 months, benzoyl peroxide should be utilized for at least 5–7 days between antibiotic courses to avoid resistance.[17,20] Combination treatment with different types of oral and topical antibiotics should be avoided.[17,77]

Another potential strategy for reducing the spread of antibiotic-resistant strains may be to eliminate the use of antibiotics

Table II. Trials of dapsone, azelaic acid, and zinc combination therapy published since 2004

Study (no. of patients)	Design	Treatment	Results	Adverse effects
Fleischer et al.[61] (n=301)	Randomized, double-blind, 12 wk study in patients with moderate acne	Dapsone 5% gel twice daily plus adapalene 0.1% gel once daily; dapsone 5% gel twice daily plus BPO 4% gel once daily; dapsone 5% gel twice daily plus moisturizer once daily	All treatment groups showed a decrease in inflammatory lesions and were not significantly different; dapsone plus adapalene showed significantly greater improvement in non-inflammatory and total lesion count vs dapsone plus moisturizer ($p<0.001$ and $p<0.004$, respectively)	Well tolerated; more adverse events in the dapsone plus adapalene group including pruritus and burning
Pazoki-Toroudi et al.[62] (n=130)	Randomized, double-blind, 12 wk study of patients with mild to moderate acne	Azelaic acid 5% and CL 2%; azelaic acid 5%; CL 2%	Combination azelaic acid and CL significantly reduced lesion counts compared with azelaic acid ($p<0.01$) or CL ($p<0.05$)	Patients significantly more satisfied with azelaic acid and CL combination; no significant difference in adverse effects among treatment groups
Pazoki-Toroudi et al.[63] (n=147)	Randomized, double-blind, 12 wk study of patients with mild to moderate acne	Azelaic acid 5% and ERY 2%; azelaic acid 5%; ERY 2%; placebo	Combination azelaic acid and ERY significantly reduced lesion counts compared with azelaic acid ($p<0.05$), ERY ($p<0.01$), or placebo ($p<0.001$)	Azelaic acid and ERY combination demonstrated fewer adverse effects than azelaic acid or ERY monotherapy
Langner et al.[64] (n=148)	Randomized, investigator-blind, multicenter, parallel-group, 12 wk study of patients aged 12–39 y with mild to moderate acne	ERY 4% and zinc acetate 1.2% twice daily; CL 1% and BPO 5% gel once daily	CL and BPO had an earlier onset of action and showed greater reductions in inflammatory lesions ($p=0.029$) as well as total lesions ($p=0.017$)	Well tolerated, mild and intermittent scaling, erythema, dryness, pruritus, and burning

BPO = benzoyl peroxide; **CL** = clindamycin; **ERY** = erythromycin.

Table III. Trials comparing BPO, topical antibiotic, and topical retinoid combination therapy published since 2004

Study (no. of patients)	Design	Treatment	Results	Adverse effects
Leyden, et al.[81] (n=30)	Open-label, single-center, 4 wk study in patients with high levels of *Propionobacterium acnes* of the facial skin including various levels of resistance to ERY, CL, and tetracycline	Adapalene 0.1% and BPO 2.5% combination gel applied to forehead once daily	Mean total *P. acnes* bacterial counts decreased significantly ($p<0.001$); resistance to *P. acnes* highest for ERY and CL; *P. acnes* resistance to all antibiotics was significantly decreased at the end of the study	Well tolerated; specific adverse effects were not commented on
Jackson et al.[82] (n=54)	Randomized, investigator-blind, two-center, parallel-group, 16 wk study in patients aged ≥12 y with moderate to moderately severe acne	Once daily: CL 1% and BPO 5%; CL 1.2% and tretinoin 0.025%	CL and BPO had greater reductions in *P. acnes* counts ($p=0.0030$); CL and BPO showed earlier onset of action; reductions in inflammatory, non-inflammatory, and total lesion counts were similar between groups by wk 16	Well tolerated; mild dryness, pruritus, burning, and peeling
Gollnick et al.[51] (n=1670)	Randomized, double-blind, transatlantic, multicenter, controlled, 12 wk study in patients aged ≥12 y with moderate acne	Once daily: adapalene 0.1% and BPO 2.5% gel; adapalene 0.1%; BPO 2.5%; vehicle control gel	Adapalene and BPO combination was significantly more effective ($p<0.001$) in decreasing percentage lesion count than either monotherapy or vehicle	Well tolerated; mild to moderate dryness
Bowman et al.[83] (n=132)	Randomized, investigator-blind, multicenter, 10 wk study in patients aged 12–30 y with mild to moderate acne	CL 1% and BPO 5% gel once daily; tretinoin 0.025% gel plus CL 1% gel once daily; CL 1% and BPO 5% gel in the morning and tretinoin 0.025% gel plus CL 1% gel in the evening	CL and BPO group and CL and BPO plus tretinoin group had significantly greater reduction in inflammatory lesions than tretinoin plus CL group ($p=0.05$ and $p=0.02$, respectively)	Well tolerated; mild to moderate irritation and dryness; substantially more adverse events reported for combination regimen than either regimen alone; overall more adverse effects with tretinoin-containing regimens

BPO = benzoyl peroxide; **CL** = clindamycin; **ERY** = erythromycin.

altogether and combine other topical agents. Benzoyl peroxide in combination with topical retinoids is one option, as neither retinoids nor benzoyl peroxide creates selective pressure for resistance. While there have been some trials evaluating the efficacy and tolerability of this approach, there is limited evidence of its effect on microbial resistance.[78,79] A randomized, double-blind study of combination adapalene and benzoyl peroxide therapy in patients with moderate to moderately severe acne found that lesion count was significantly improved in the group treated with adapalene 0.1% and benzoyl peroxide 2.5% compared with either agent alone or placebo.[75,80] The frequency of adverse events and cutaneous tolerability for adapalene and benzoyl peroxide were comparable to that observed with adapalene monotherapy, although resistance was not specifically addressed.[75,80] A small open-label study evaluated the effectiveness of combination adapalene 0.1% and benzoyl peroxide 2.5% in reducing antibiotic-sensitive and -resistant strains of *P. acnes* on the facial skin of study subjects. All subjects had strains sensitive and resistant to erythromycin, clindamycin, and tetracyclines at baseline. Mean counts of erythromycin-, clindamycin-, and tetracycline-resistant *P. acnes* were significantly decreased by week 4[81] (see table III).

9. Treatment Selection

9.1 Expert Guidelines

There is expert consensus that combination therapies are more efficacious and less susceptible to bacterial resistance than monotherapy alone.[4,75,84] All of these guidelines illustrate similar approaches in which initial therapy selection is

based on the severity and inflammatory nature of the lesions[17] (see table IV).

The guidelines differ, however, in their recommendations regarding selection of topical medications.[4,38,75,76,85] Practical advice on how to manage acne based upon a systematic search of evidence is provided by the NHS Clinical Knowledge Summaries (CKS) guideline[38] from the UK, including treatment options for mild to severe disease (see table IV).

9.2 Comparing Combination Therapies

As noted in a 2003 expert report, there is a need to perform well controlled trials comparing benzoyl peroxide with the newer topical retinoids.[20] Indeed, there are few robust studies comparing various combination regimens of benzoyl peroxide, clindamycin, and retinoids (see table III).

One study[82] evaluated the efficacy of clindamycin 1.2% and tretinoin 0.025% gel with clindamycin 1% and benzoyl peroxide 5% gel. While the clindamycin and benzoyl peroxide combination group had a faster reduction in inflammatory and total lesion counts compared with the tretinoin combination group, reduction in inflammatory, non-inflammatory, and total acne lesions were similar by the end of the 16-week study.[82] Reductions in clindamycin-resistant *P. acnes* colonization occurred only in the benzoyl peroxide group, but overall reduction in disease severity was comparable at 87% for the tretinoin combination group and 80% for the benzoyl peroxide combination group.[82]

A relatively small, single-blind study of patients with mild to moderate acne[83,86] compared the efficacy of tretinoin 0.025% and clindamycin 1% gel once daily versus benzoyl peroxide 5% and clindamycin 1% gel once daily versus benzoyl peroxide 5% and clindamycin 1% applied in the morning with tretinoin 0.025% plus clindamycin 1% applied in the evening. Treatment groups with benzoyl peroxide (benzoyl peroxide and clindamycin, and benzoyl peroxide and clindamycin plus tretinoin) had significantly greater reductions in inflammatory lesions as well as greater reductions in non-inflammatory lesions at week 10. All three regimens were safe and generally well tolerated, although agents with tretinoin initially caused more irritation, dryness, desquamation, and erythema. It has been suggested that these results should be viewed with caution as there were

Table IV. Summary of current treatment guidelines for acne

Group	Mild	Moderate	Severe
UK National Health Service Clinical Knowledge Summary[38]	First line: topical retinoid or BPO monotherapy	First line: BPO + topical antibiotic combination (monotherapy if non-inflammatory)	First line: oral antibiotics and referral for oral isotretinoin
	Second line: topical antibiotic or azelaic acid monotherapy	Second line: BPO + topical retinoid or topical retinoid + topical antibiotic	Second line: adjunct topical BPO or topical retinoid
		For truncal acne or poor tolerance of topical treatment try oral antibiotic	Avoid topical antibiotics with oral antibiotics
		Consider azelaic acid if above treatments poorly tolerated	
American Academy of Dermatology[4]	First line: topical BPO, retinoids, or antibiotic monotherapy	First line: combination therapy of BPO, topical retinoid or topical antibiotic	First line: oral antibiotics or oral isotretinoin
	Second line: azelaic acid or salicylic acid monotherapy	Second line: oral tetracyclines. ERY, CL, or TMP-SMX if patient is pregnant	Second line: hormonal agents, referral to specialist
Global Alliance to Improve Outcomes in Acne[75]	First line: topical retinoid (+ topical antimicrobial if inflammatory)	First line: oral antibiotic + topical retinoid ± BPO (if nodular)	First line: oral isotretinoin
	Second line: alternate topical retinoid ± topical antimicrobial or azelaic acid or salicylic acid	Second line: oral isotretinoin (if nodular) or alternate antibiotic + alternate retinoid ± BPO or azelaic acid, oral antiandrogens (women)	Second line: high-dose oral antibiotic + topical retinoid + BPO, oral antiandrogens (women)
Institute for Clinical Systems Improvement[5]	Topical BPO + antibiotic (inflammatory) or topical retinoid (non-inflammatory)	First line: topical BPO + antibiotic or oral isotretinoin Second line: topical retinoid or oral antibiotic	First line: oral isotretinoin, referral

BPO = benzoyl peroxide; **CL** = clindamycin; **ERY** = erythromycin; **TMP-SMX** = trimethoprim/sulfamethoxazole (cotrimoxazole).

significant differences in the baseline characteristics of the groups and significant loss to follow-up.[38]

A randomized, double-blind study conducted in 2003 compared treatment groups receiving either benzoyl peroxide 5% and erythromycin 3% or tretinoin 0.025% and erythromycin 4% topical gels each applied twice daily. The number of papules, pustules, and comedones was reduced in the two treatment groups at week 12, with no significant differences between groups. Physician rating of improvement was significantly higher in the benzoyl peroxide and erythromycin group compared with the tretinoin and erythromycin group; however, there was no significant difference in patient ratings between the two treatment groups. The benzoyl peroxide and erythromycin group also demonstrated significantly less erythema and scaling, as evaluated by patients and the study physician, compared with tretinoin and erythromycin. The authors concluded that for moderate acne vulgaris, benzoyl peroxide and erythromycin may provide a greater beneficial effect than tretinoin and erythromycin.[87]

Another relatively small, single-blind study evaluated combination benzoyl peroxide 5% and clindamycin 1% versus adapalene 0.1% in patients with mild to moderate acne.[45] The clindamycin and benzoyl peroxide group exhibited earlier onset of action with significantly greater reductions in total lesions and inflammatory lesions than the adapalene group. While both treatments were well tolerated, benzoyl peroxide and clindamycin generally caused fewer adverse effects.

9.3 Adverse Effects

Localized adverse effects including erythema, desquamation, itching, burning, and general skin sensitivity directly impact compliance.[5,7,9] Patients should be counselled to expect initial irritation and should be advised to discontinue treatment if irritation becomes severe. To avoid adverse effects, topical treatment is generally initiated at low concentrations and applied as a thin layer to the affected surface area with the patients advised to wash their hands after application.[5,7]

Where irritation persists, a change in preparation to washes, gels, moisturizing creams, or lotions may help.[17] Water-based preparations of benzoyl peroxide may cause less skin irritation than the alcohol-based solutions.[11,17] Alcohol-based preparations are more drying and therefore more suitable for oilier skin.[16,17] Leave-on preparations of benzoyl peroxide have similar efficacy but demonstrate a positive correlation between dose and irritation.[11,88] Percutaneous absorption and irritation may be minimized by the use of benzoyl peroxide washes, as they may not damage the epidermal barrier function.[11,88] It should also be noted that while combining antibiotics, retinoids, and benzoyl peroxide together can be slightly more efficacious, this combination can also lead to an increase in skin irritation and potentially decreased compliance.[86] Sequential treatment is thus recommended (e.g. benzoyl peroxide and antibiotic treatment in the morning, retinoids in the evening).[17,86]

There have been no data suggesting benzoyl peroxide has any relationship to the development of skin cancer in humans.[89] While considered safe for use by pregnant women, benzoyl peroxide is categorized within category C by the US FDA although there is no reported evidence suggesting human fetal risk.[9] Erythromycin and clindamycin fall within pregnancy category B as animal studies have demonstrated no adverse effects to the fetus but similar human studies do not exist.[90] Any treatment containing tetracyclines or retinoids should be avoided during pregnancy. Pseudomembranous colitis has been reported with topical clindamycin use.[91] Patients and their parents should be made aware that benzoyl peroxide can bleach clothing, towels, bed linens, and perhaps even hair.[11,17]

9.4 Cost

Providers and patients must also weigh costs and drug availability in choosing a treatment regimen.[66] The average total cost of treatment per episode across all age groups is $US689.06.[92] Topical retinoids ($US40 to >$US100 per 30-day supply) are in general more expensive than generic benzoyl peroxide preparations ($US21 to $US60 per 30-day supply).[5,10] When administered separately but coincidentally, the cost of benzoyl peroxide and a topical antibiotic is higher than benzoyl peroxide by itself, but much lower than proprietary fixed-dose combination therapy.[8] A price comparison in 2006 showed that the cost of purchasing benzoyl peroxide and an antibiotic as separate agents ranged between $US21 and $US60 for 1 month of therapy, in contrast to $US61 to $US100 for a month's supply of the fixed-dose combination therapy of benzoyl peroxide and an antibiotic.[5] A 2004 trial showed that benzoyl peroxide monotherapy is similar in efficacy to combined erythromycin and benzoyl peroxide treatment and was judged to be the most cost-effective therapy, although it produced greater skin irritation.[46,49] Erythromycin and benzoyl peroxide administered separately were nearly three times more cost effective than the proprietary fixed-dose combination.[46,49] Erythromycin and clindamycin (generic) both cost in the range of $US21 to $US41 per 30-day supply but clindamycin has the advantage of not requiring refrigeration as it is stable at room temperature.[10,25]

9.5 Practical Considerations

Although individual generic preparations used concomitantly may be more cost effective, compliance may be increased with once-daily combination products because of convenience and faster speed of onset.[10,92] Higher concentrations of erythromycin require refrigeration,[25] thus dermatologists sometimes prefer the fixed-dose combination of benzoyl peroxide 5% and clindamycin 1%.

When using topical antibiotics for acne, physicians should consider local patterns of resistance and select the shortest feasible treatment duration. Data indicate that 6–8 weeks is an appropriate timepoint to assess response to antibiotic treatment.[17,46] If acne fails to respond to topical treatments, it is advisable to verify patient adherence to the recommended treatment regimen. If adherence to treatment is adequate, expert guidelines recommend considering increasing the drug strength and or frequency of application, combining different topical products, or starting an oral therapy. Where there is poor adherence to treatment due to intolerance of topical treatments, Clinical Knowledge Summaries from the UK National Health Service recommend reducing the strength of treatment, using a different preparation of the drug, or switching to an alternative topical agent that causes less irritation.[8,38]

The use of benzoyl peroxide for truncal acne was reviewed in a recent study, utilizing a 5.3% emollient. This study showed that a brief application (5 minutes) of the solution followed by a shower demonstrated clinical benefit. This brief application avoided the bleaching effects of the medication on clothing and suggested that compliance would be enhanced when large areas such as the shoulders or chest could have the medication removed after this short interval.[93] Patients with back acne may respond better to oral antibiotic therapy, however, because of the practical difficulty of applying treatment to a large, inaccessible area.[6]

9.6 Conflicts of Interest

For further details of the conflicts of interest statements for studies published since 2004, see the table in Supplemental Digital Content 2, http://links.adisonline.com/DYZ/A4.[2] All self-reported conflicts of interest were included. Additionally, the Propublica Dollars for Docs Database was searched by author for additional conflicts of interests and all results were included even when duplicative.[94] It is important to note that the Propublica Dollars for Docs Database is not a complete listing of all drug company contributions and the information is largely limited to 2009, 2010, and 2011.[94] It is possible that an author could have a new conflict of interest that did not exist when the associated article was published. The intent of the SDC 2 is to provide this information to practitioners and not to imply that a particular author failed to disclose a conflict of interest.

10. Conclusion

Antibiotics, retinoids, and benzoyl peroxide have complementary mechanisms of action, which makes combination treatment attractive from the standpoint of efficacy, tolerability, and decreased bacterial resistance. Definitive, randomized, controlled trials comparing the efficacy, safety, and cost of adapalene, benzoyl peroxide, and clindamycin alone and in various combinations remain to be accomplished. Robust studies comparing cost and efficacy of generic combinations of these agents compared with proprietary fixed-dose combination therapies are also lacking. Azelaic acid, sodium sulfacetamide, dapsone, and zinc are potential agents that may also be combined with the above-named medications for the treatment of mild to moderate acne, although the evidence supporting their use is limited.

Acknowledgments

This project was funded in part by the Department of Veterans Affairs (Dr Dellavalle). The opinions expressed in this article represent those of the authors and not of the US government. The authors would like to thank Lilian Hoffecker for her contribution to this work.

Dr Dellavalle's institution (the University of Colorado) received an unrestricted educational grant from Galderma Pharmaceuticals and Abbott Pharmaceuticals for a conference on comparative effectiveness research in dermatology held at the University of Colorado School of Medicine in 2010. He also receives royalties as a dermatology section editor at UpToDate. The other authors have no conflicts of interest to declare.

References

1. Thiboutot D, Gollnick H, Bettoli V, 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 (5 Suppl.): S1-50
2. Tan HH. Topical antibacterial treatments for acne vulgaris: comparative review and guide to selection. Am J Clin Dermatol 2004; 5 (2): 79-84
3. Brown SK, Shalita AR. Acne vulgaris. Lancet 1998; 351 (9119): 1871-6
4. Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007; 56 (4): 651-63
5. Institute for Clinical Systems Improvement. Neely C, Davis M, Lee J, et al. ICSI acne guidelines, 2006 [online]. Available from URL: http://www.icsi.org/acne/acne_management_3.html [Accessed 2011 Apr 17]
6. Patel M, Bowe WP, Heughebaert C, et al. The development of antimicrobial resistance due to the antibiotic treatment of acne vulgaris: a review. J Drugs Dermatol 2010; 9 (6): 655-64
7. Purdy S, de Berker D. Acne vulgaris. Clin Evid (Online). Epub 2011 Apr 12

8. What role for topical antibacterials in acne? Drug Ther Bull 2010; 48 (12): 141-4
9. Dutil M. Benzoyl peroxide: enhancing antibiotic efficacy in acne management. Skin Therapy Lett 2010; 15 (10): 5-7
10. Krakowski AC, Stendardo S, Eichenfield LF. Practical considerations in acne treatment and the clinical impact of topical combination therapy. Pediatr Dermatol 2008; 25 Suppl. 1: 1-14
11. Fakhouri T, Yentzer BA, Feldman SR. Advancement in benzoyl peroxide-based acne treatment: methods to increase both efficacy and tolerability. J Drugs Dermatol 2009; 8 (7): 657-61
12. Del Rosso JQ, Kim GK. Topical antibiotics: therapeutic value or ecologic mischief? Dermatol Ther 2009; 22 (5): 398-406
13. Del Rosso JQ, Leyden JJ, Thiboutot D, et al. Antibiotic use in acne vulgaris and rosacea: clinical considerations and resistance issues of significance to dermatologists. Cutis 2008; 82 (2 Suppl. 2): 5-12
14. Leyden JJ, Del Rosso JQ, Webster GF. Clinical considerations in the treatment of acne vulgaris and other inflammatory skin disorders: focus on antibiotic resistance. Cutis 2007; 79 (6 Suppl.): 9-25
15. Tan AW, Tan HH. Acne vulgaris: a review of antibiotic therapy. Expert Opin Pharmacother 2005; 6 (3): 409-18
16. Simonart T, Dramaix M. Treatment of acne with topical antibiotics: lessons from clinical studies. Br J Dermatol 2005; 153 (2): 395-403
17. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. Lancet. Epub 2011 Aug 29
18. Chivot M. Retinoid therapy for acne. A comparative review. Am J Clin Dermatol 2005; 6 (1): 13-9
19. Thiboutot D, Arsonnaud S, Soto P. Efficacy and tolerability of adapalene 0.3% gel compared to tazarotene 0.1% gel in the treatment of acne vulgaris. J Drugs Dermatol 2008; 7 (6 Suppl.): s3-10
20. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol 2003; 49 (1 Suppl.): S1-37
21. Gollnick H, Schramm M. Topical therapy in acne. J Eur Acad Dermatol Venereol 1998; 11 Suppl. 1: S8-12; discussion S28-9
22. Leyden JJ. A review of the use of combination therapies for the treatment of acne vulgaris. J Am Acad Dermatol 2003; 49 (3 Suppl.): S200-10
23. Mills OH, Kligman AM. Treatment of acne vulgaris with topically applied erythromycin and tretinoin. Acta Derm Venereol 1978; 58 (6): 555-7
24. Martin B, Meunier C, Montels D, et al. Chemical stability of adapalene and tretinoin when combined with benzoyl peroxide in presence and in absence of visible light and ultraviolet radiation. Br J Dermatol 1998; 139 Suppl. 52: 8-11
25. 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 (4): 590-5
26. Bojar RA, Eady EA, Jones CE, et al. Inhibition of erythromycin-resistant propionibacteria on the skin of acne patients by topical erythromycin with and without zinc. Br J Dermatol 1994; 130 (3): 329-36
27. Mills OH, Kligman AM, Pochi P, et al. Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. Int J Dermatol 1986; 25 (10): 664-7
28. Lyons RE. Comparative effectiveness of benzoyl peroxide and tretinoin in acne vulgaris. Int J Dermatol. 1978; 17 (3): 246-51
29. 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 (3): 165-8
30. Bucknall JH, Murdoch PN. Comparison of tretinoin solution and benzoyl peroxide lotion in the treatment of acne vulgaris. Curr Med Res Opin 1977; 5 (3): 266-8
31. Handojo I. Retinoic acid cream (Airol cream) and benzoyl-peroxide in the treatment of acne vulgaris. Southeast Asian J Trop Med Public Health 1979; 10 (4): 548-51
32. Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. Pediatrics 2006; 118 (3): 1188-99
33. Weinberg JM. The utility of benzoyl peroxide in hydrophase base (Brevoxyl) in the treatment of acne vulgaris. J Drugs Dermatol 2006; 5 (4): 344-9
34. Sawleshwarkar SN, Salgaonkar V, Oberai CM. Multicenter study to evaluate efficacy and irritation potential of benzoyl peroxide 4% cream in hydrophase base (Brevoxyl) in acne vulgaris. Indian J Dermatol Venereol Leprol 2003; 69 (1): 19-22
35. Gold LS. Fixed-combination products in the management of acne vulgaris. Cutis 2010; 85 (3): 160-7
36. Gold MH. A multicenter efficacy and tolerability evaluation of benzoyl peroxide in a 10% urea vehicle for the treatment of acne vulgaris. J Drugs Dermatol 2006; 5 (5): 442-5
37. Jelvehgari M, Siahi-Shadbad MR, Azarmi S, et al. The microsponge delivery system of benzoyl peroxide: preparation, characterization and release studies. Int J Pharm 2006; 308 (1-2): 124-32
38. UK National Health Service Clinical Knowledge Summary. Acne vulgaris, 2009 [online]. Available from URL: http://www.cks.nhs.uk/search?&page=1&q=acne%20vulgaris&site=0 [Accessed 2011 Apr 13]
39. Kinney MA, Yentzer BA, Fleischer AB, et al. Trends in the treatment of acne vulgaris: are measures being taken to avoid antimicrobial resistance? J Drugs Dermatol 2010; 9 (5): 519-24
40. Chalker DK, Shalita A, Smith JG, et al. A double-blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. J Am Acad Dermatol 1983; 9 (6): 933-6
41. Tschen E. Potential role for a new combination topical therapy in treating mild to moderate acne vulgaris. Cutis 2001; 67 (2 Suppl.): 25-7
42. Leyden J. Are 2 combined antimicrobial mechanisms better than 1 for the treatment of acne vulgaris? Clinical and antimicrobial results of a topical combination product containing 1% clindamycin and 5% benzoyl peroxide. Introduction Cutis 2001; 67 (2 Suppl.): 5-7
43. Thiboutot D, Zaenglein A, Weiss J, et al. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients. J Am Acad Dermatol 2008; 59 (5): 792-800
44. Kircik L, Green L, Thiboutot D, et al. Comparing a novel solubilized benzoyl peroxide gel with benzoyl peroxide/clindamycin: final data from a multicenter, investigator-blind, randomized study. J Drugs Dermatol 2009; 8 (9): 812-8
45. Langner A, Chu A, Goulden V, et al. A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide and adapalene in the treatment of mild to moderate facial acne vulgaris. Br J Dermatol 2008; 158 (1): 122-9
46. Ozolins M, Eady EA, Avery AJ, et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. Lancet 2004; 364 (9452): 2188-95
47. Seidler E, Kimball AB. Meta-analysis of randomized controlled trials using 5% benzoyl peroxide and clindamycin versus 2.5% benzoyl peroxide and clindamycin topical treatments in acne [abstract]. J Am Acad Dermatol 2011; 64 (2): AB6
48. Bucks D, Angel A, Del Rosso J, et al. Can delivery be enhanced and skin irritation minimized using a lower concentration of benzoyl peroxide in a fixed combination product [abstract]? J Am Acad Dermatol 2009; 60 (3): AB16
49. Ozolins M, Eady EA, Avery A, et al. Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne. Health Technol Assess 2005; 9 (1): iii-212
50. Wolf JE, Kaplan D, Kraus SJ, et al. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blinded study. J Am Acad Dermatol 2003; 49 (3 Suppl.): S211-7
51. Gollnick HP, Draelos Z, Glenn MJ, et al. Adapalene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients. Br J Dermatol 2009; 161 (5): 1180-9

52. NilFroushzadeh MA, Siadat AH, Baradaran EH, et al. Clindamycin lotion alone versus combination lotion of clindamycin phosphate plus tretinoin versus combination lotion of clindamycin phosphate plus salicylic acid in the topical treatment of mild to moderate acne vulgaris: a randomized control trial. Indian J Dermatol Venereol Leprol 2009; 75 (3): 279-82
53. Rietschel RL, Duncan SH. Clindamycin phosphate used in combination with tretinoin in the treatment of acne. Int J Dermatol 1983; 22 (1): 41-3
54. Leyden JJ, Krochmal L, Yaroshinsky A. Two randomized, double-blind, controlled trials of 2219 subjects to compare the combination clindamycin/tretinoin hydrogel with each agent alone and vehicle for the treatment of acne vulgaris. J Am Acad Dermatol 2006; 54 (1): 73-81
55. Leyden J, Wortzman M, Baldwin EK. Tolerability of clindamycin/tretinoin gel vs. tretinoin microsphere gel and adapalene gel. J Drugs Dermatol 2009; 8 (4): 383-8
56. Draelos Z, Tanghetti E. Optimizing the use of trazarotene for the treatment of facial acne vulgaris: a multicenter, double-blinded, randomized parallel-group trial. Cutis 2002; 69 (2 Suppl.): 20-29
57. Tanghetti E, Dhawan S, Torok H, et al. Tazarotene 0.1 percent cream plus clindamycin 1 percent gel versus tretinoin 0.025 percent gel plus clindamycin 1 percent gel in the treatment of facial acne vulgaris. Dermatol Online J 2007; 13 (3): 1
58. Brand B, Gilbert R, Baker MD, et al. Cumulative irritancy comparison of adapalene gel 0.1% versus other retinoid products when applied in combination with topical antimicrobial agents. J Am Acad Dermatol 2003; 49 (3 Suppl.): S227-32
59. Draelos ZD, Carter E, Maloney JM, et al. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. J Am Acad Dermatol. 2007; 56 (3): 439.e1-10
60. Piette WW, Taylor S, Pariser D, et al. Hematologic safety of dapsone gel, 5%, for topical treatment of acne vulgaris. Arch Dermatol 2008; 144 (12): 1564-70
61. Fleischer AB, Shalita A, Eichenfield LF, et al. Dapsone gel 5% in combination with adapalene gel 0.1%, benzoyl peroxide gel 4% or moisturizer for the treatment of acne vulgaris: a 12-week, randomized, double-blind study. J Drugs Dermatol 2010; 9 (1): 33-40
62. Pazoki-Toroudi H, Nilforoushzadeh MA, Ajami M, et al. Combination of azelaic acid 5% and clindamycin 2% for the treatment of acne vulgaris. Cutan Ocul Toxicol 2011 Dec; 30 (4): 286-91
63. Pazoki-Toroudi H, Nassiri-Kashani M, Tabatabaie H, et al. Combination of azelaic acid 5% and erythromycin 2% in the treatment of acne vulgaris. J Dermatolog Treat 2010; 21 (3): 212-6
64. Langner A, Sheehan-Dare R, Layton A. A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide (Duac) and erythromycin + zinc acetate (Zineryt) in the treatment of mild to moderate facial acne vulgaris. J Eur Acad Dermatol Venereol 2007; 21 (3): 311-9
65. Draelos ZD. The multifunctionality of 10% sodium sulfacetamide, 5% sulfur emollient foam in the treatment of inflammatory facial dermatoses. J Drugs Dermatol 2010; 9 (3): 234-6
66. Seidler EM, Kimball AB. Meta-analysis comparing efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin in acne. J Am Acad Dermatol 2010; 63 (1): 52-62
67. Graupe K, Cunliffe WJ, Gollnick HP, et al. Efficacy and safety of topical azelaic acid (20 percent cream): an overview of results from European clinical trials and experimental reports. Cutis 1996; 57 (1 Suppl.): 20-35
68. Thiboutot D. Versatility of azelaic acid 15% gel in treatment of inflammatory acne vulgaris. J Drugs Dermatol 2008; 7 (1): 13-6
69. Burkhart CG, Burkhart CN. Treatment of acne vulgaris without antibiotics: tertiary amine-benzoyl peroxide combination vs. benzoyl peroxide alone (Proactiv Solution). Int J Dermatol 2007; 46 (1): 89-93
70. Eady AE, Cove JH, Layton AM. Is antibiotic resistance in cutaneous propionibacteria clinically relevant? Implications of resistance for acne patients and prescribers. Am J Clin Dermatol 2003; 4 (12): 813-31
71. Eady EA, Gloor M, Leyden JJ. Propionibacterium acnes resistance: a worldwide problem. Dermatology 2003; 206 (1): 54-6
72. Cooper AJ. Systematic review of Propionibacterium acnes resistance to systemic antibiotics. Med J Aust 1998; 169 (5): 259-61
73. Coates P, Vyakrnam S, Eady EA, et al. Prevalence of antibiotic-resistant propionibacteria on the skin of acne patients: 10-year surveillance data and snapshot distribution study. Br J Dermatol 2002; 146 (5): 840-8
74. Ross JI, Snelling AM, Carnegie E, et al. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol 2003; 148 (3): 467-78
75. Thiboutot D, Gollnick H, Bettoli V, 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 (5 Suppl.): S1-50
76. Nast A, Bayerl C, Borelli C, et al. S2k-guideline for therapy of acne [in German]. J Dtsch Dermatol Ges 2010; 8 Suppl. 2: s1-59
77. Patel M, Bowe WP, Heughebaert C, et al. The development of antimicrobial resistance due to the antibiotic treatment of acne vulgaris: a review. J Drugs Dermatol 2010; 9 (6): 655-64
78. Handojo I. The combined use of topical benzoyl peroxide and tretinoin in the treatment of acne vulgaris. Int J Dermatol 1979; 18 (6): 489-96
79. Shalita AR, Rafal ES, Anderson DN, et al. Compared efficacy and safety of tretinoin 0.1% microsphere gel alone and in combination with benzoyl peroxide 6% cleanser for the treatment of acne vulgaris. Cutis 2003; 72 (2): 167-72
80. Thiboutot DM, Weiss J, Bucko A, et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. J Am Acad Dermatol 2007; 57 (5): 791-9
81. Leyden JJ, Preston N, Osborn C, et al. In-vivo effectiveness of adapalene 0.1%/benzoyl peroxide 2.5% gel on antibiotic-sensitive and resistant Propionibacterium acnes. J Clin Aesthet Dermatol 2011; 4 (5): 22-6
82. Jackson JM, Fu JJ, Almekinder JL. A randomized, investigator-blinded trial to assess the antimicrobial efficacy of a benzoyl peroxide 5%/clindamycin phosphate 1% gel compared with a clindamycin phosphate 1.2%/tretinoin 0.025% gel in the topical treatment of acne vulgaris. J Drugs Dermatol 2010; 9 (2): 131-6
83. Bowman S, Gold M, Nasir A, et al. Comparison of clindamycin/benzoyl peroxide, tretinoin plus clindamycin, and the combination of clindamycin/benzoyl peroxide and tretinoin plus clindamycin in the treatment of acne vulgaris: a randomized, blinded study. J Drugs Dermatol 2005; 4 (5): 611-8
84. Nast A, Dreno B, Bettoli V, et al. European evidence based (S3) guideline for treatment of acne (ICD L70.0). EU Acne Guidelines Group; draft version 13/5/2011 [online]. Available from URL: http://www.acne-guideline.com/home_eu/External_open_review/ [Accessed 2011 May 28]
85. Acne Working Group. Management of mild and moderate acne vulgaris. GP Review 2008 Jan 1-11
86. Alexis AF. Clinical considerations on the use of concomitant therapy in the treatment of acne. J Dermatolog Treat 2008; 19 (4): 199-209
87. Gupta AK, Lynde CW, Kunynetz RA, et al. A randomized, double-blind, multicenter, parallel group study to compare relative efficacies of the topical gels 3% erythromycin/5% benzoyl peroxide and 0.025% tretinoin/erythromycin 4% in the treatment of moderate acne vulgaris of the face. J Cutan Med Surg 2003; 7 (1): 31-7
88. Burkhart CG, Scheinfeld NS. Benzoyl peroxide skin washes: basis, logic, effectiveness, and tolerance. Skinmed 2005; 4 (6): 370
89. Kraus AL, Munro IC, Orr JC, et al. Benzoyl peroxide: an integrated human safety assessment for carcinogenicity. Regul Toxicol Pharmacol 1995; 21 (1): 87-107
90. Rothman KF, Pochi PE. Use of oral and topical agents for acne in pregnancy. J Am Acad Dermatol 1988; 19 (3): 431-42

91. Parry MF, Rha CK. Pseudomembranous colitis caused by topical clindamycin phosphate. Arch Dermatol 1986; 122 (5): 583-4

92. Yentzer BA, Ade RA, Fountain JM, et al. Simplifying regimens promotes greater adherence and outcomes with topical acne medications: a randomized controlled trial. Cutis 2010; 86 (2): 103-8

93. Bikowski J. A review of the safety and efficacy of benzoyl peroxide (5.3%) emollient foam in the management of truncal acne vulgaris. J Clin Aesthet Dermatol 2010; 3 (11): 26-9

94. Nguyen D, Ornstein C, Weber T. Dollars for docs: how industry dollars reach your doctors [online]. Available from URL: http://projects.propublica.org/docdollars/ [Accessed 2011 Sep 15]

Correspondence: Dr *Robert P. Dellavalle*, Chief, Dermatology Service, Department of Veteran Affairs Medical Center, 1055 Clermont Street, Box 165, Denver, CO 80220, USA.
E-mail: robert.dellavalle@ucdenver.edu