Quality and Safety in Practice Committee

Acne: Management in Primary Care

Author:
Dr Johnny Loughnane

12 February 2019

Acne Management in Primary Care

Quick Reference Guide

Quality and Safety in Practice Committee

AUTHOR

Dr Johnny Loughnane GP

Disclaimer and Waiver of Liability

Whilst every effort has been made by the Quality and Safety in Practice Committee to ensure the accuracy of the information and material contained in this document, errors or omissions may occur in the content. This guidance represents the view of the ICGP which was arrived at after careful consideration of the evidence available at time of publication.

This quality of care may be dependent on the appropriate allocation of resources to practices involved in its delivery. Resource allocation by the state is variable depending on geographical location and individual practice circumstances. There are constraints in following the guidelines where the resources are not available to action certain aspects of the guidelines. Therefore, individual healthcare professionals will have to decide what is achievable within their resources particularly for vulnerable patient groups.

The guide does not however override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of individual patients in consultation with the patient and/or guardian or carer.

Guidelines are not policy documents. Feedback from local faculty and individual members on ease of implementation of these guidelines is welcomed.

ICGP Quality in Practice Committee 2016

Dr Paul Armstrong
Dr Patricia Carboy
Dr Regina Codd
Dr Harry Comber
Dr Mary Kearney
Dr Niamh Moran
Dr Maria O'Mahony
Dr Ben Parmeter
Dr Philip Sheeran Purcell
Dr Patrick Redmond

External Review: An external review of this document was kindly carried out by Dr Anne-Marie Tobin Consultant Dermatologist Tallaght Hospital and Clinical Senior Lecturer at TCD.

Correspondence to: qip@icgp.ie

Potential conflicts of interest of authors

The author has provided consultancy services to GSK, Galderma and Leo Pharma, has received assistance in attending conferences from GSK, Galderma and Leo Pharma and has received speaker fees from GSK, Astellas, Galderma and Leo Pharma.

Evidence-Based Medicine

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.

In a systematic review of clinical practice guidelines on the management of acne published from 2007 to 2013 five guidelines were identified and reviewed. (1)

The European Evidence-Based Guidelines for the Treatment of Acne guidelines (ES3) were found to combine the highest methodologic quality with a detailed description of the search methodology and explicit disclosure of the process leading to specific recommendations. (2) It has been decided to adapt the ES3 guidelines to reflect the Irish health care system. The recently published Canadian clinical practice guideline on acne updated the literature search from March 2010 (the end date of the ES3 literature search) to March 2013. (3) Updated evidence from the Canadian guideline was included in the adapting process. The guidelines are developed in accordance with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (4) and the ADAPTE framework (5) for guideline adaptation.

Many different grading systems for assessing the quality of evidence are available in the field of guideline development. The ES3 guidelines used the grading system adopted for the European Psoriasis Guidelines with some adaptations taken from the GRADE system. (2)

A 10% difference in efficacy (lesion reduction) was taken as demonstrating superior efficacy and considered relevant. (2)

A grade of evidence was given to every individual trial included:

a) Randomized, double-blind clinical trial of high quality.
b) Randomized clinical trial of lesser quality.
c) Comparative trial with severe methodological limitations.

When looking at a specific question (e.g. efficacy of BPO relative to adapalene) the available evidence was summarized by aligning a level of evidence (LE) using the following criteria:

1. Further research is very unlikely to change our confidence in the estimate of effect. At least two trials are available that were assigned a grade of evidence A and the results are predominantly consistent with the results of additional grade B or C studies.
2. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. At least three trials are available that were assigned a grade of evidence B and the results are predominantly consistent with respect to additional grade C trials.
3. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Conflicting evidence or limited amount of trials, mostly with a grade of evidence of B or C.
4. Any estimate of effect is very uncertain. Little or no systematic empirical evidence; included trials are extremely limited in number and/or quality.

The European evidence-based guidelines for the treatment of acne assigned a “strength of recommendation” grade to weigh the different recommendations. (2) All aspects of the treatment decision, such as efficacy, safety, patient preference and the reliability of the existing body of evidence (level of evidence) were considered in assigning grades. Recommendation are allocated a low, medium or high strength. (2)

Table of Contents

Section 1: Introduction

1.1 Aims of the Document

The aims of this document are to:

1. Offer advice on appropriate therapy options, according to the type of acne present in the patient
2. Improve the quality and consistency of acne therapy in primary care
3. Allow patients, in consultation with their general practitioner, make an informed choice on best therapy for their acne
4. Reduce the risk of scarring
5. Encourage general practitioners to explore the psychological effects of acne for the patient
6. Improve adherence with treatment regimens
7. Reduce antibiotic resistance
8. Advise on the range of products available in the Irish market

1.2 Disease Activity

To give treatment recommendations based on disease activity, the ES3 guidelines classify acne as follows:

1. Comedonal acne
2. Mild–moderate papulopustular acne
3. Severe papulopustular acne, moderate nodular acne
4. Severe nodular acne, conglobate acne

Key Points/Recommendations

1. The vast majority of acne patients can be managed in primary care. To provide this treatment general practitioners need to be up to date on the latest evidence regarding the management of acne.
2. Treatment targeted at as many of the pathogenic mechanisms as possible gives best outcomes
3. Always assess the psychological impact of acne
4. Consider topical combination products as first line therapy for patients presenting with mild to moderate mixed acne

1.3 What is Acne?

Acne is a disease of the pilosebaceous units of the skin which are predominantly found on the face, upper back and anterior chest. (6) A hyper-responsive reaction of these pilosebaceous units to androgen leads to the development of acne. Most acne patients have normal levels of circulating androgen. It is a polymorphic eruption presenting with non-inflamed comedones (blackheads and whiteheads) and inflammatory papules, pustules and nodules. Seborrhoea is frequent. (7) The majority of patients presenting for treatment have a mixture of inflamed and non-inflamed acne. (8)

Acne affects about 80% of the population between ten and thirty years of age. (9) Many, with more mild disease, will not consult their doctor. It tends to be more persistent in females. (9) Males tend to have more severe disease with higher risk of scarring. Over time disease activity waxes and wanes.

Peak incidence in females is between 13 to 16 years and between 15 and 18 years in males. Acne persists for 8 to 10 years on average. This chronic course is important to recognise as both patient and doctor need to commit to a prolonged management course.

Acne scarring is common. (10) Deep pustules, nodules and to a lesser extent superficial pustules may scar. Scarring is associated with either collagen loss (ice-pick scare, atrophic scars or box car scars) or increase in collagen. (hypertrophic scars or keloid scars). Inadequately treated acne can result in permanent physical scarring. Once established, scarring, is very difficult to treat. (11) The best predictor of future scarring is scarring that is already present. Scarring is best prevented by starting appropriate anti-inflammatory medication, when indicated, without delay. Antibiotics have the best anti-inflammatory effect and an oral preparation is usually appropriate from the start if scarring is already evident. Patients with scarring should be advised to return at any time if they feel the condition is worsening, despite good adherence, for consideration of more aggressive therapy.

Acne is a disease common in adolescence and young adulthood and is a very visible condition. Unsurprisingly it often has an intense emotional impact. Acne has been documented to be associated with depression, anxiety, social phobia and even suicide. (12) Patients with mild to moderate acne have a higher rate of suicidal ideation than their peers suffering from other chronic, severe skin diseases.

Section 2: Treatment Options

2.1 Topical applications

Benzyl peroxide (BPO)

BPO is an antibacterial agent that kills P acnes, has an anti-inflammatory effect and is also mildly comedolytic. (13) Bacterial resistance does not develop. (14) Adding BPO to regimens of antibiotic therapy enhances results and may reduce the development of bacterial resistance. It may cause a mild irritant dermatitis (erythema and scaling). The risk of this is reduced by gradually increasing the time BPO is left on the skin, before washing it off. To start with, leave it on for one hour. It may bleach hair and clothes and cause contact allergy. There is little or no benefit from increasing potency above 5%, only an increased risk of irritation (15, 16)

Recommendations for BPO.

- Recommended for use alone or in a fixed combination product with clindamycin.
- As it prevents bacterial resistance recommended for concurrent use in patients on topical or systemic antibiotic therapy.

Retinoids

There are three topical retinoids available. Tretinoin, is available as 0.01% gel and 0.025% lotion. Isotretinoin is available as 0.05 % gel and adapalene is available as 0.1% gel and cream. Evidence from randomized, double-blind, placebo-controlled trials supports their use for acne treatment. (17, 18) Retinoids mainly work by normalising desquamation of follicular epithelium, leading to loosening of the keratin plug. Retinoids are thereby effective in both the treatment and prevention of comedones. In addition they facilitate the penetration of other topical medications, such as antibiotics. Adapalene also has anti-inflammatory effects. (19) Retinoids reduce post inflammatory hyperpigmentation in patients with dark skin.

Topical retinoids are the treatments of choice for non-inflamed acne i.e. open and closed comedones. For mixed non-inflammed and inflamed acne a fixed combination of clindamycin phosphate 1.2%/tretinoin 0.025% gel is effective. (20,21) A topical retinoid may be used to maintain clearance after discontinuation of oral therapy.

The main side effect of topical retinoids is skin irritation resulting in erythema, dryness, and peeling. Irritation may be mitigated by reduced frequency of application or by gradually increasing the time the retinoid is left on the skin, before washing it off. To start with, leave it on for one hour. (22) Topical retinoids may cause photosensitivity and therefore are best applied at night. Advice on sunscreen use should be given. They are not licensed for use pregnancy. Contraceptive cover should be considered in female patients. There may be an initial, temporary flare of acne lesions after starting a topical retinoid. Topical retinoids should not be used in combination with oral isotretinoin.

Recommendations for topical retinoids:

- Topical retinoids are first line treatments in primarily comedonal acne.
- Topical retinoids should be combined with topical or oral antibiotics in patients with mixed inflammatory and non-inflammatory acne lesions.

A fixed dose combination product combines the actions of BPO and adapalene in a once daily application. As it does not contain an antibiotic there is no risk no developing bacterial resistance.

Azelaic Acid

Azelaic acid is available as a 15% gel. It has anti-inflammatory action secondary to its antimicrobial effect. It also has some limited anti-comedogenic action. Bacteria do not develop resistance to azelaic acid. It may reduce post-inflammatory hyperpigmentation in dark skinned patients. It does not tend to irritate making it useful in patients with sensitive skin. (23, 24, 25) Azelaic acid is safe to use in pregnancy. Studies have shown it to be comparable to benzyl peroxide, topical retinoids and topical antibiotics. (26)

Recommendation for azelaic acid:

- Azelaic acid is recommended in inflamed and non-inflamed acne, especially in patients with sensitive skin who may be intolerant of other topical products.
- Azelaic acid is recommended in the treatment of post inflammatory hyperpigmentation

Topical Antibiotics

Clindamycin 1% solution or gel is now the only "antibiotic-only" topical antibiotic available in Ireland.

Topical antibiotics have anti-inflammatory and antibacterial effects, making them an effective treatment option in acne (27) Topical antibiotics should not be used alone when treating acne as there is a risk of antibiotic resistance developing. They are best used in combination with BPO. This increases efficacy and decreases the risk of developing of bacterial resistance. Topical erythromycin is more likely to induce bacterial resistance than clindamycin. (27,28,29,30,31)

Combination therapies available are – erythromycin 3%/BPO 5%, Clindamycin 1%/BPO 5%, clindamycin 1.2%/ tretinoin 0.025% gel, and erythromycin/isotretinoin. (32,33,34,35) Combination agents may enhance compliance with treatment regimens. Clindamycin and erythromycin are safe in pregnancy.

The majority of acne patients presenting in primary care have mild to moderate, mixed acne. They will have both inflamed and non-inflamed lesions and will respond best if as many aspects of the disease as possible are targeted. Fixed combination products allow this and apart from improved efficacy they are convenient and enhance treatment adherence. (36)

Recommendations for topical antibiotics:

- Topical antibiotics are not recommended as monotherapy because of the risk of bacterial resistance.
- Topical antibiotics are effective acne treatments when used in combination with either BPO or a topical retinoid.

2.2 Systemic Antibiotics

Systemic antibiotics have an antibacterial and a strong anti-inflammatory action. They are indicated for use in moderate to severe inflammatory acne. Monotherapy with systemic antibiotic should be avoided due to the risk of developing bacterial resistance. They should be used in combination with a topical retinoid if noninflamed lesions predominate and BPO if inflamed lesions predominate. (37, 38) Combination of lymecycline and adapalene shows superior efficacy compared with lymecycline monotherapy. (39)

The tetracycline class of antibiotics are considered first-line therapy for moderate to severe acne. Lymecycline, in a dose of 300 milligrams daily, is the preferred choice. Previously minocycline was considered to be more effective than lymecycline or doxycycline. (40) A Cochrane review found minocycline to be no more effective than other antibiotics in the treatment of acne. (41) More serious adverse events are reported with minocycline compared to other tetracyclines. (41, 42) These include autoimmune hepatitis, drug reaction with eosinophilia and systemic symptoms, and lupus. (43,44,45) If minocycline is used for longer than 6 months monitoring is required for liver, autoimmune and pigmentation problems. This should include a clinical examination and blood tests for liver function and an autoimmune screen. This should be repeated every 3 months. Minocycline may cause a blue-grey discoloration especially of inflamed skin.

Patients taking a systemic tetracycline should be warned to report any persisting headache, visual field defects or diplopia. Benign intracranial hypertension is rare but can be anything but benign. Prompt cessation of treatment greatly reduces the risk of permanent visual impairment.

Erythromycin has been widely used to treat acne. However the risk of developing bacterial resistance is greater for erythromycin than for other antibiotics. If a systemic antibiotic is indicated in pregnancy erythromycin is a safe option. All tetracyclines should be avoided in pregnancy.

Tetracyclines should be avoided during breast feeding. They are not licensed in Ireland for children less than 12 years of age because of the risk of enamel hypoplasia.

Recommendations on systemic antibiotics:

- Lymecycline is recommended in the management of moderate and severe acne and in mild inflammatory acne with inadequate response to topical treatments.
- Doxycycline may be used but is not superior to lymecycline.
- Monotherapy with systemic antibiotics is not recommended.
- Erythromycin may be used during pregnancy and children under 12 years of age.
- Trimethoprim may be used for patients who are intolerant or unresponsive to tetracyclines.
- Systemic antibiotic use should be limited to the shortest possible duration, typically 3 months, to minimize the development of bacterial resistance.
- Topical therapy with BPO or a retinoid should always be advised when taking systemic antibiotics.
- When the systemic antibiotic is stopped the topical therapy should be continued as maintenance therapy.
-

Antibiotic Resistance

Antibiotic resistance is a growing problem leading to calls to limit the duration of antibiotic courses and to promote the use of combined regimens. (46) Resistance is greatest to erythromycin followed by clindamycin. (47) There are increasing reports of failure to respond to treatment due to the development of antibiotic resistance. (47,48,49) Adding a retinoid or BPO therapy to antibiotic therapy improves treatment outcomes. (50,51,52)

While antibiotic use should be limited to the shortest possible duration, typically 3 months, to minimize the development of bacterial resistance, there is a subset of patients for whom alternative therapies are inappropriate and who may require a longer course of either systemic or oral antibiotics. (53) The need for antibiotic therapy in these patients should be regularly reviewed after three months therapy to ensure they are not continued for longer than is necessary. Once antibiotics are stopped topical maintenance regimens should be advised.

Topical, non-antibiotic therapies can accomplish continued efficacy months after the discontinuation of antibiotics. (51,54,55) The AAD guideline group agrees that such maintenance is paramount to reducing antibiotic resistance. (53, 56) Patients should be advised that they may have to remain on these applications for up to 6 years or more.

Recommendations on antibiotic resistance:

- Review the need for continuing an antibiotic after 3 to 4 months of therapy to minimize the development of bacterial resistance.
- Never combine topical and systemic antibiotics.
- When antibiotic treatment is finished continuing benzyl peroxide helps eradicate resistant bacteria that may have emerged during antibiotic treatment.
- Topical retinoid preparations are recommended as maintenance therapy.

2.3 Hormonal Treatment

Adult women, in different age categories, have a significantly higher prevalence of acne than adult men. (57) The prevalence of adult female acne is rising. (58) Combination oral contraceptive pills (COCs) contain both an oestrogen and a progestin component. Progestins have a varying androgenic potential. The second-generation progestin levonorgestrel tends to be more androgenic but when combined with ethinyl oestradiol, the net effect is usually antiandrogenic. (59) Oral contraceptives are an effective treatment for adult female acne. (60,61,62,63) Because of limited evidence, it is difficult to recommend which COC gives consistently superior results when treating acne. (64, 65) Progestins with low androgenic activity (desogestrel) or anti-androgenic activity (cyproterone acetate, drospiranone) are preferred. (66) Ethinylestradiol combined with cyproterone acetate has superior efficacy compared with ethinylestradiol combined with levonorgestrel (67,68,69) Ethinylestradiol combined with cyproterone acetate shows superior efficacy compared with tetracycline. (70) Antibiotics may be superior at 3 months but COCs are equivalent to antibiotics at 6 months in reducing acne lesions and, thus, may be a better first-line alternative to systemic antibiotics for long-term acne management in women. (68)

In recent years there has been much debate regarding the relative risk of thrombosis with different COC preparations. Recent research has shown drosperinone and cyproterone acetate to have similar relative risks to desogestrel and gestodene i.e.1.6-1.8 times greater than with levonorgestrel. (71) The absolute increased risks give a clearer reflection of the thrombosis risk.

Table 1: VTE risk/ 10,000 women-years

	VTE risk/ 10,000 women-years
Non contraceptive users, not pregnant	2
Ethinylestradiol + levonorgestrel, norgestimate or norethisterone	5-7
Etonogestrel (ring), norelgestromin patch	6-12
Ethinylestradiol + gestodene, Desogestrel or drospirenone	9-12
Pregnancy	5 – 20
Within 12 weeks postpartum	40 – 65

COCs take 3 or more months to work. (60,61,62,63) Therefore, consideration should be given to combining COCs with other acne treatments, as outlined in previous sections, for the first three to six months of therapy, especially if any scarring is already evident.

Tetracyclines do not reduce the effectiveness of COCs when taken concomitantly.

The combination of an anti-androgen, cyproterone acetate (2mg) plus ethinyl oestradiol (35 microgram) is licensed in Ireland for the treatment of severe acne in women. It is not licensed for the sole purpose of oral contraception.

Recommendations on hormonal treatment:

- Oestrogen-containing combined oral contraceptives are effective and recommended in the treatment of inflammatory acne in females.

2.4 Diet

There is some evidence that a low glycaemic diet may reduce acne severity. (72) There is also limited evidence to suggest that some dairy products, particularly skim milk, may adversely affect acne. (73)

Recommendations for the role of diet in acne:

- In view of the limited evidence available, specific dietary changes are not recommended in the management of acne.
- Overweight patients should be advised to use a low glycaemic diet.

2.5 Summary of Treatment Recommendations

COMEDONAL	MILD TO MODERATE PAPULOPUSTULAR	SEVERE PAPULOPUSTULAR- MILD NODULAR	NODULAR
Topical retinoid (M) **BPO (L)** **AZELAIC ACID (L)**	**BPO + ADAPALENE (fc) (H)** **BPO + CLINDAMYCIN (fc) (H)** **TRETINOIN + CLINDAMYCIN (fc) (M)** **BPO am and TOPICAL RETINOID pm (L)** **INADEQUATE RESPONSE** **SYSTEMIC ANTIBIOTIC + TOPICAL RETINOID (L)** **SYSTEMIC ANTIBIOTIC + BPO + ADAPALENE (FC) (L)**	**REFER FOR ISOTRETINOIN (H) *** **SYSTEMIC ANTIBIOTIC + TOPICAL RETINOID (M)** **SYSTEMIC ANTIBIOTIC + AZELAIC ACID (M)** **Systemic antibiotic + BPO + ADAPALENE (fc) (M)** **SYSTEMIC ANTIBIOTIC + BPO (L)** **INADEQUATE RESPONSE** **REFER FOR ISOTRETINOIN (H)** **ALTERNATIVE FOR FEMALES** **ANTIANDROGENIC COC + TOPICAL RETINOID or BPO or AZELAIC ACID (L)** **ANTIANDROGENIC COC + SYSTEMIC ANTIBIOTIC (L)**	**REFER FOR ISOTRETINOIN (H)*** **SYSTEMIC ANTIBIOTIC + TOPICAL RETINOID (L)** **SYSTEMIC ANTIBIOTIC + BPO (L)** **ALTERNATIVE FOR FEMALES** **ANTIANDROGENIC COC + SYSTEMIC ANTIBIOTIC (L)**

BPO + benzyl peroxide, fc = fixed combination product, COC = combined oral contraceptive

Systemic antibiotic = lymecycline or doxycycline

*When referring for isotretinoin it is recommended to also start appropriate systemic antibiotic plus topical therapy.

L = low strength recommendation, M = medium strength recommendation, H = high strength recommendation

References

1. Kawala C, Fernando D, Tan JK. Quality appraisal of acne clinical practice guidelines, 2008–2013. J Cutan Med Surg 2014;18:385-91).
2. Nast A, Dreno B, Bettoli V, Degitz K, Erdmann R, Finlay AY, et al. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol 2012;26 (suppl 1):1-29
3. Asai Y, Baibergenova A, Dutil M et al. Management of acne: Canadian clinical practice guideline. CMAJ 2015. DOI:10.1503/cmaj.140665.
4. Brouwers M, Kho ME, Browman GP, et al.; AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ 2010,182:E839-42.
5. The ADAPTE process: resource toolkit for guideline adaptation. ADAPTE Collaboration; 2009. Available: www.g-i-n.net
6. Cunliffe WJ. The Acnes. Martin Dunitz Ltd, London, 1989.
7. Cunliffe WJ, Shuster S. Pathogenesis of acne. Lancet 1969; 1: 685–687.
8. Tan JK. The Canadian acne epidemiological survey: baseline demographics and interim analysis. J Am Acad Dermatol 2004;50:15.
9. Goulden V, Stables GI, Cunliffe WJ. Prevalence of facial acne in adults. J Am Acad Dermatol 1999; 41: 577–580.
10. Layton AM, Henderson CA, Cunliffe WJ. A clinical evaluation of acne scarring and its incidence. Clin Exp Dermatol 1994; 19: 303–308.
11. Purdy S, de Berker D. Acne BMJ 2006; 333 :949.
12. Barnes LE, Levender MM, Fleischer AB Jr, Feldman SR. Quality of life measures for acne patients. Dermatol Clin 2012;30:293-300.
13. Fulton JE Jr, Farzad-Bakshandeh A, Bradley S. Studies on the mechanism of action to topical benzoyl peroxide and vitamin A acid in acne vulgaris. J Cutan Pathol. 1974;1:191-200.
14. Gamble R, Dunn J, Dawson A, Petersen B, McLaughlin L, Small A, et al. Topical antimicrobial treatment of acne vulgaris: an evidence-based review. Am J Clin Dermatol2012;13:141-52.
15. Fyrand O, Jakobsen HB. Water-based versus alcohol-based benzoyl peroxide preparations in the treatment of acne vulgaris. Dermatologica. 1986;172:263-267.
16. 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;25:664-667.
17. Krishnan G. Comparison of two concentrations of tretinoin solution in the topical treatment of acne vulgaris. Practitioner. 1976;216:106-109.
18. Bradford LG, Montes LF. Topical application of vitamin A acid in acne vulgaris. South Med J. 1974;67:683-687.
19. Ingram JR, Grindlay DJ, Williams HC. Management of acne vulgaris: an evidence-based update. Clin Exp Dermatol2010;35:351-4.
20. Richter JR, Bousema MT, De Boulle KLV, Degreef HJ, Poli F. Efficacy of a fixed clindamycin phosphate 1.2%, tretinoin 0.025% gel formulation (Velac) in the topical control of facial acne lesions. J Dermatolog Treat. 1998;9:81-90.
21. Zouboulis CC, Derumeaux L, Decroix J, Maciejewska-Udziela B, Cambazard F, Stuhlert A. A multicentre, single-blind, randomized comparison of a fixed clindamycin phosphate/tretinoin gel formulation (Velac) applied once daily and a clindamycin lotion formulation (Dalacin T) applied twice daily in the topical treatment of acne vulgaris. Br J Dermatol. 2000;143:498-505.
22. Pedace F.J., and Stoughton R.: Topical retinoic acid in acne vulgaris. Br J Dermatol 1971; 84: pp. 465-469

23. Kircik LH. Efficacy and safety of azelaic acid (AzA) gel 15% in the treatment of post-inflammatory hyperpigmentation and acne: a 16-week, baseline-controlled study. J Drugs Dermatol. 2011;10:586-590.
24. Cunliffe WJ, Holland KT. Clinical and laboratory studies on treatment with 20% azelaic acid cream for acne. Acta Derm Venereol Suppl (Stockh). 1989;143:31-34.
25. Katsambas A, Graupe K, Stratigos J. Clinical studies of 20% azelaic acid cream in the treatment of acne vulgaris. Comparison with vehicle and topical tretinoin. Acta Derm Venereol Suppl (Stockh). 1989;143:35-39.
26. Iraji F, Sadeghinia A, Shahmoradi Z, Siadat AH, Jooya A. Efficacy of topical azelaic acid gel in the treatment of mild-moderate acne vulgaris. Indian J Dermatol Venereol Leprol2007;73:94-6. 1.
27. Mills O Jr, Thornsberry C, Cardin CW, Smiles KA, Leyden JJ. Bacterial resistance and therapeutic outcome following three months of topical acne therapy with 2% erythromycin gel versus its vehicle. Acta Derm Venereol. 2002;82:260-265.
28. Shalita AR, Smith EB, Bauer E. Topical erythromycin v clindamycin therapy for acne. A multicenter, double-blind comparison. Arch Dermatol. 1984;120:351-355.
29. 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: 822-827.
30. Kuhlman DS, Callen JP. A comparison of clindamycin phosphate 1 percent topical lotion and placebo in the treatment of acne vulgaris. Cutis. 1986;38:203-206.
31. Becker LE, Bergstresser PR, Whiting DA, et al. Topical clindamycin therapy for acne vulgaris. A cooperative clinical study. Arch Dermatol. 1981;117:482-485.
32. Leyden JJ, Hickman JG, Jarratt MT, Stewart DM, Levy SF. The efficacy and safety of a combination benzoyl peroxide/ clindamycin topical gel compared with benzoyl peroxide alone and a benzoyl peroxide/erythromycin combination product. J Cutan Med Surg. 2001;5:37-42.
33. Tschen EH, Katz HI, Jones TM, et al. A combination benzoyl peroxide and clindamycin topical gel compared with benzoyl peroxide, clindamycin phosphate, and vehicle in the treatment of acne vulgaris. Cutis. 2001;67:165-169.
34. Schlessinger J, Menter A, Gold M, et al. Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. J Drugs Dermatol 2007;6:607-15.
35. Dreno B, Bettoli V, Ochsendorf F et al. Efficacy and safety of clindamycin phosphate 1.2%/tretinoin 0.025% formulation for the treatment of acne vulgaris: pooled analysis of data from three randomised, double-blind, parallel-group, phase III studies). Eur J Dermatol 2014; 24: 201–209
36. 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: 73–81.
37. Tan J, Humphrey S, Vender R, et al. A treatment for severe nodular acne: a randomized investigator-blinded, controlled, noninferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs. oral isotretinoin. Br J Dermatol. 2014;171:1508-1516.
38. Zaenglein AL, Shamban A, Webster G, et al. A phase IV, open-label study evaluating the use of triple-combination therapy with minocycline HCl extended-release tablets, a topical antibiotic/retinoid preparation and benzoyl peroxide in patients with moderate to severe acne vulgaris. J Drugs Dermatol. 2013;12:619-625.
39. Cunliffe WJ, Meynadier J, Alirezai M et al. Is combined oral and topical therapy better than oral therapy alone in patients with moderate to moderately severe acne vulgaris? A comparison of the efficacy and safety of lymecycline plus adapalene gel 0.1%, versus lymecycline plus gel vehicle. J Am Acad Dermatol 2003; 49: S218–S226.
40. Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007;56: 651-663.

41. Garner SE, Eady A, Bennett C, Newton JN, Thomas K, Popescu CM. Minocycline for acne vulgaris: efficacy and safety. Cochrane Database Syst Rev. 2012;(8):CD002086.
42. Lebrun-Vignes B, Kreft-Jais C, Castot A, Chosidow O, French Network of Regional Centers of Pharmacovigilance. Comparative analysis of adverse drug reactions to tetracyclines: results of a French national survey and review of the literature. Br J Dermatol. 2012;166:1333-1341.
43. Kermani TA, Ham EK, Camilleri MJ, Warrington KJ. Polyarteritis nodosa-like vasculitis in association with minocycline use: a single-center case series. Semin Arthritis Rheum. 2012;42:213-221.
44. Shaughnessy KK, Bouchard SM, Mohr MR, Herre JM, Salkey KS. Minocycline-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with persistent myocarditis. J Am Acad Dermatol. 2010;62: 315-318.
45. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. Clin Ther. 2005;27:1329-1342.
46. Thiboutot D, Gollnick H, Bettoli V, Dreno B, Kang S, Leyden JJ, et al. New insights into the management of acne: an update from the global alliance to improve outcomes in acne group. J Am Acad Dermatol2009;60(5 suppl):S1-50).
47. Ross JI, Snelling AM, Carnegie E et al. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol 2003; 148: 467–478.
48. 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 Dermatol2006;54:73-81.
49. Eady EA, Cove JH, Holland KT, Cunliffe WJ. Erythromycin resistant propionibacteria in antibiotic treated acne patients: association with therapeutic failure. Br J Dermatol 1989; 121: 51–57.
50. Lookingbill DP, Chalker DK, Lindholm JS, Katz HI, Kempers SE, Huerter CJ, 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 Dermatol1997;37:590-5
51. Thiboutot DM, Shalita AR, Yamauchi PS, et al. Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris: a randomized, controlled, investigator-blind follow-up of a recent combination study. Arch Dermatol. 2006;142: 597-602.
52. Poulin Y, Sanchez NP, Bucko A, et al. A 6-month maintenance therapy with adapalene-benzoyl peroxide gel prevents relapse and continuously improves efficacy among patients with severe acne vulgaris: results of a randomized controlled trial. Br J Dermatol. 2011;164:1376-1382.
53. Zaenglein AL, Path AL, Schlosser BJ et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol 2016;74:945-973.
54. Gold LS, Cruz A, Eichenfield L, et al. Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. Cutis. 2010;85:94-104.
55. Tan J, Stein Gold L, Schlessinger J, et al. Short-term combination therapy and long-term relapse prevention in the treatment of severe acne vulgaris. J Drugs Dermatol. 2012;11:174-180.
56. Moon SH, Roh HS, Kim YH, et al. Antibiotic resistance of microbial strains isolated from Korean acne patients. J Dermatol. 2012;39:833-837.
57. Collier CN, Harper JC, Cafardi JA et al. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol 2008; 58: 56–59.
58. Kim GK, Michaels BB. Post-adolescent acne in women: more common and more clinical considerations. J Drugs Dermatol 2012; 11: 708–713
59. Arrington EA, Patel NS, Gerancher K, Feldman SR. Combined oral contraceptives for the treatment of acne: a practical guide. Cutis. 2012;90:83-90.
60. Lucky AW, Koltun W, Thiboutot D, et al. A combined oral contraceptive containing 3-mg drospirenone/20-microg ethinyl estradiol in the treatment of acne vulgaris: a randomized, double-

blind, placebo-controlled study evaluating lesion counts and participant self-assessment. Cutis. 2008;82:143-150.

61. Maloney JM, Dietze P Jr, Watson D, et al. Treatment of acne using a 3-milligram drospirenone/20-microgram ethinyl estradiol oral contraceptive administered in a 24/4 regimen: a randomized controlled trial. Obstet Gynecol. 2008;112:773-781.
62. Maloney JM, Dietze P Jr, Watson D, et al. A randomized controlled trial of a low-dose combined oral contraceptive containing 3 mg drospirenone plus 20 microg ethinylestradiol in the treatment of acne vulgaris: lesion counts, investigator ratings and subject self-assessment. J Drugs Dermatol. 2009;8:837-844.
63. Plewig G, Cunliffe WJ, Binder N, Hoschen K. Efficacy of an oral contraceptive containing EE 0.03 mg and CMA 2 mg (Belara) in moderate acne resolution: a randomized, double-blind, placebo-controlled phase III trial. Contraception. 2009;80: 25-33
64. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. Cochrane Database Syst Rev. 2012;(6):CD004425.
65. Palli MB, Reyes-Habito CM, Lima XT, Kimball AB. A single-center, randomized double-blind, parallel-group study to examine the safety and efficacy of 3mg drospirenone/0.02 mg ethinyl estradiol compared with placebo in the treatment of moderate truncal acne vulgaris. J Drugs Dermatol. 2013;12: 633-637.
66. Williams C, Layton AM. Persistent acne in women: implications for the patient and for therapy. Am J Clin Dermatol 2006; 7: 281–290
67. Carlborg L. Cyproterone acetate versus levonorgestrel combined with ethinyl estradiol in the treatment of acne. Results of a multicentre study. Acta Obstet Gynecol Scand Suppl 1986; 134: 29–32.
68. Koo EB, Petersen TD, Kimball AB. Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris. J Am Acad Dermatol 2014; 71(3): 450-9.
69. Wishart JM. An open study of Triphasil and Diane 50 in the treatment of acne. Australas J Dermatol 1991; 32: 51–54.
70. Greenwood R, Brummitt L, Burke B, Cunliffe WJ. Acne: double blind clinical and laboratory trial of tetracycline, oestrogen-cyproterone acetate, and combined treatment. Br Med J (Clin Res Ed) 1985; 291: 1231–1235.
71. George R, Clarke S, Thiboutot D. Hormonal therapy for acne. Semin Cutan Med Surg. 2008;27:188-196.
72. Smith RN, Mann NJ, Braue A, Makelainen H, Varigos GA. The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. J Am Acad Dermatol2007;57:247-56.CrossRefMedlineWeb of Science
73. Spencer EH, Ferdowsian HR, Barnard ND. Diet and acne: a review of the evidence. Int J Dermatol 2009;48:339-47.