

# CME

Follow the link from the online version of this article to obtain certified continuing medical education credits

# Acne vulgaris

Annelise L Dawson,<sup>1</sup> Robert P Dellavalle<sup>2,3,4</sup>

<sup>1</sup>Department of Internal Medicine, Brigham and Women's Hospital, Boston, MA, USA

<sup>2</sup>Department of Dermatology, University of Colorado Denver, Aurora, Colorado, USA

<sup>3</sup>Dermatology Service, Department of Veterans' Affairs Medical Center, Denver, CO 80220, USA

<sup>4</sup>Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Aurora, CO, USA

Correspondence to: R P Dellavalle, Dermatology Service, Department of Veteran Affairs Medical Center, Denver, CO, USA  
robert.dellavalle@ucdenver.edu

Cite this as: *BMJ* 2013;346:f2634  
doi: 10.1136/bmj.f2634

Acne vulgaris is a common inflammatory skin condition. Although often perceived as a self limited disease of adolescence, its prevalence remains high into adulthood. Nearly 90% of teenagers have acne, and half of them continue to experience symptoms as adults.<sup>1-3</sup> By age 40 years, 1% of men and 5% of women still have lesions.<sup>4</sup> Recent analyses show an increasing prevalence of acne in children, perhaps because of pubertal onset.<sup>5</sup>

Given that acne may persist for decades and require long term therapy, there has been a recent effort to reclassify acne as a chronic disease.<sup>2,6</sup> Acne has clear detrimental psychosocial effects and may lead to permanent scarring.<sup>7</sup> It is therefore not surprising that patients are motivated to seek medical care. In the United Kingdom, acne accounts for more than 3.5 million annual visits to general practitioners,<sup>3,8</sup> who must therefore be equipped to treat acne. Several prominent groups—including the Global Alliance to Improve Outcomes in Acne, the European Dermatology Forum, and the American Academy of Dermatology—have published comprehensive treatment recommendations detailing comparable therapeutic strategies.<sup>9-11</sup> Here we provide a streamlined outline of treatment intended for the non-specialist.

## What are the clinical characteristics of acne?

A spectrum of lesions may be present, including non-inflammatory open and closed comedones (blackheads and whiteheads, respectively) and inflammatory papules, pustules, nodules, and cysts. Lesions may be present on the face, neck, chest, or back—areas with the greatest density of pilosebaceous units.<sup>12</sup> Comedone formation is intrinsic to the diagnosis of acne vulgaris—when not clinically apparent, consider alternative diagnoses. Diseases that mimic acne include rosacea, folliculitis, angiofibromas, perioral dermatitis, and keratosis pilaris.<sup>5,13,14</sup> The patient's age may also help to distinguish these disorders from acne. Keratosis pilaris and perioral dermatitis, for example, tend to present in childhood, whereas rosacea tends to affect older adults. In cases of diagnostic uncertainty, referral to specialist care is warranted.

## SUMMARY POINTS

Do not underestimate the impact of acne on patient quality of life and mental health

Topical retinoids are now a mainstay of treatment

Avoid prolonged antibiotic courses and antibiotic monotherapy because of the risk of bacterial resistance

For women with refractory acne or lesions confined to the lower half of the face, consider the addition of combined oral contraceptives

Oral isotretinoin is the most effective treatment for severe acne

Assess treatment adherence, which may be limited by irritation or regimen complexity

## SOURCES AND SELECTION CRITERIA

We performed a Medline database search using the term “acne” together with “antibiotic resistance”, “antibiotics”, “azelaic acid”, “benzoyl peroxide”, “classification”, “depression”, “diet”, “epidemiology”, “isotretinoin”, “oral contraceptives”, “pathogenesis”, “retinoids”, “scarring”, “smoking”, “treatment”, “treatment guidelines”, and “vulgaris.” We also searched the *Cochrane Database of Systematic Reviews* using the term “acne”.

Several groups have proposed standardized measures for classifying acne, although none has been universally accepted.<sup>10,13,15</sup> Classification is important because it helps to inform treatment strategies.<sup>3,11</sup> Acne is categorized broadly into mild, moderate, and severe forms. Mild acne is typically limited to the face and is characterized by the presence of non-inflammatory closed and open comedones with few inflammatory lesions. Moderate acne is characterized by an increased number of inflammatory papules and pustules on the face and often mild truncal disease. Finally, acne is considered to be severe when nodules and cysts are present. In these cases, facial lesions are often accompanied by widespread truncal disease.

## What causes acne?

Acne is an inflammatory disease of the pilosebaceous duct that results from four primary pathophysiologic processes:

- Abnormal keratinocyte proliferation and desquamation that leads to ductal obstruction
- Androgen driven increase in sebum production
- Proliferation of *Propionibacterium acnes*
- Inflammation.<sup>2,9,13,16,17</sup>

Increased androgen production causes abnormal epithelial desquamation and follicular obstruction, which lead to the primary precursor lesion in acne—the microcomedone. Microcomedones are pathological structures not visible to the naked eye that evolve into visible lesions.<sup>18</sup> An increase in circulating androgens also promotes sebum production, causing these obstructed follicles to fill with lipid rich material and form visible open and closed comedones.<sup>12,19</sup> Sebum serves as a substrate for bacterial growth, leading to proliferation of *P acnes*. Finally, *P acnes* releases chemical mediators that promote inflammation, which is propagated by traumatic rupture of comedones into the surrounding dermis.<sup>2,17</sup> This inflammation manifests through the development of inflammatory papules, pustules, nodules, and cysts.

The successful management of acne requires an understanding of these four facets of the pathophysiology of acne. Clinicians should select mechanistically driven treatment regimens that target each patient's predominant lesion types.

## Can acne be prevented?

Myths about the causes of acne abound. The central discoloration in blackheads is not dirt, but oxidized melanin.<sup>20</sup> A

## bmj.com

Previous articles in this series

▶ Adolescent idiopathic scoliosis  
(*BMJ* 2013;346:f2508)

▶ Diagnosis and management of hidradenitis suppurativa  
(*BMJ* 2013;346:f2121)

▶ Pulmonary hypertension: diagnosis and management  
(*BMJ* 2013;346:f2028)

▶ Leukaemia update. Part 2: managing patients with leukaemia in the community  
(*BMJ* 2013;346:f1932)

▶ Leukaemia update. Part 1: diagnosis and management  
(*BMJ* 2013;346:f1660)

comprehensive systematic review found little evidence for an association between acne and poor facial hygiene and provided minimal support for frequent face washing.<sup>21</sup> Aggressive cleansing may cause irritation, thereby exacerbating active lesions or limiting the patient's tolerance of therapy.<sup>21 22</sup> Basic care with twice daily washing and use of a moisturizer that does not contribute to comedone formation (noncomedogenic) is an accepted standard.<sup>9</sup> Although misconceptions about dietary triggers have been largely dispelled, recent reports—including a systematic review of dietary influences on acne and a randomized investigator masked controlled trial of glycemic load and acne severity—suggest that acne is associated with high dairy diets and those with a high glycemic load.<sup>23-27</sup> Finally, a cross sectional analysis found a significant dose dependent association between smoking and acne severity.<sup>20 28</sup>

**How is acne treated?**

Careful assessment of the morphology and severity of acne is an important first step in management, because lesion morphology largely dictates the optimal treatment approach. Treatment should be designed to target precursor lesions (microcomedones) and active inflammatory lesions. Milder cases are best managed with topical regimens, whereas systemic drugs are indicated in more severe cases. The box summarises the mechanisms of action of the most commonly used agents. The table provides a treatment framework based on disease severity.

**Topical agents**

**Retinoids**

Retinoids are vitamin A derivatives that normalize keratinocyte desquamation and adhesion, leading to comedolysis and preventing formation of new microcomedones. Some retinoids also display anti-inflammatory properties.<sup>11 15 29-32</sup> Perhaps the most notable recent development in the treatment of acne is the increased use of topical retinoids.<sup>29</sup> Many randomized trials show the efficacy of these drugs relative to vehicle, and they are recommended for all cases of acne, except when oral retinoids are used.<sup>9 11</sup> Studies show improvements within weeks, with maximal benefit after three to four months.<sup>13 15 18</sup> Mild non-inflammatory comedonal acne may be treated with retinoid monotherapy. When inflammatory lesions are present, retinoids should be combined with antimicrobial therapy or benzoyl peroxide.<sup>9 16</sup> Because retinoids prevent the development of microcomedones, they can also

**Effects of the different agents used to treat acne**

- Topical retinoids: Comedolytic and sometimes anti-inflammatory
- Antibiotics: Antimicrobial and anti-inflammatory
- Benzoyl peroxide: Antimicrobial plus weakly anti-inflammatory and comedolytic
- Hormonal agents: Sebosuppressive
- Oral retinoids: Comedolytic, sebosuppressive, antimicrobial, and anti-inflammatory

be used for maintenance therapy.<sup>9</sup>

Several topical retinoid products exist, including tretinoin, isotretinoin (not available in the United States), adapalene, and tazarotene (not licensed for treatment of acne in the United Kingdom).<sup>18</sup> These products are available in cream, gel, liquid, and microsphere formulations, each at multiple concentrations. Formulations vary by country.<sup>9 18</sup> Use of retinoids is limited by transient skin irritation, which may be prevented by selecting lower concentration or cream based formulations.<sup>18 29 31</sup> A meta-analysis of five randomized controlled trials suggests that adapalene is the best tolerated retinoid, whereas several moderately sized randomized studies found tazarotene to be most efficacious at the expense of irritation.<sup>13 18 29 31-38</sup> In addition, anecdotal evidence suggests that some patients experience an initial "flare" in acne lesions, which subsides with continued use.<sup>2 18 31</sup> Lastly, pregnant and breastfeeding women should avoid topical retinoids.<sup>18</sup> Women of child bearing age should be counselled about the need for contraception.<sup>17</sup>

**Topical antibiotics**

The primary topical antibiotics used for acne are clindamycin and erythromycin.<sup>30</sup> These agents have bacteriostatic and anti-inflammatory properties.<sup>11 30 32</sup> Topical antibiotics are used for mild to moderate acne when inflammatory lesions are present.<sup>16</sup>

Antibiotic resistance is a growing concern and has prompted efforts to limit the duration of antibiotic courses and to emphasize combined regimens.<sup>2</sup> Patterns of *P acnes* resistance correspond to trends in antibiotic use.<sup>2 39</sup> Treatment outcomes worsen when resistance is present—systematic reviews show decreasing antibiotic efficacy over time, particularly for erythromycin and clindamycin.<sup>2 32 40 41</sup> *P acnes* resistance is not the only concern—*Staphylococcus* and *Streptococcus* resistance may also develop.<sup>39 42</sup> In practice, this means avoiding antibiotic monotherapy and mainte-

Severity	Topical retinoid	Benzoyl peroxide	Topical antibiotic	Oral antibiotic	Hormonal agent*	Azelaic acid	Oral retinoid†
Maintenance	Recommended treatment	Possible treatment	No	No	Possible treatment	No	No
Mild	Recommended treatment	Possible treatment	No	No	No	Alternative treatment	No
Mild-moderate	Recommended treatment	Possible treatment	Recommended treatment	No	No	Alternative treatment	No
Moderate	Recommended treatment	Recommended treatment	Recommended treatment‡		Possible treatment	Alternative treatment	Monotherapy†
Moderate-severe	Recommended treatment	Recommended treatment	No	Recommended treatment	Possible treatment	Alternative treatment	Monotherapy†
Severe	No	No	No	No	No	No	Monotherapy†

\*Female patients only.  
 †Oral retinoids are prescribed as monotherapy.  
 ‡Select oral or topical antibiotic only.

**A PATIENT'S STORY**

I first developed acne in high school. My family encouraged me to wash my face often with several over-the-counter products, which mostly exacerbated my symptoms. I was so embarrassed about my skin that I started to avoid spending time with friends. When my mother noticed this change, she agreed to take me to a dermatologist, who suggested topical antibiotics and benzoyl peroxide. These treatments caused substantial irritation, so I stopped using them promptly. I was sure that my acne was incurable, so I learned to live with it.

When I reached adulthood, I began taking oral contraceptive pills, not knowing that they could affect the acne. Within a month of starting treatment, my acne improved dramatically. After six months, my lesions had nearly disappeared. I was thrilled to be disease free for the first time in nearly a decade but felt sad that this therapy had not been offered to me years earlier. I suspect this would have substantially improved my teenage confidence and self esteem.

nance therapy.<sup>19 20</sup> Instead, topical antibiotics should always be used with retinoids, and possibly benzoyl peroxide. Several double blind randomized controlled trials have found that the addition of retinoid or benzoyl peroxide therapy to topical antibiotics improves treatment outcomes.<sup>9 10 17 39 43 44</sup> Retinoids do not decrease resistance but promote antibiotic efficacy by improving penetration and providing synergistic comedolytic and anti-inflammatory effects.<sup>18 45</sup> Benzoyl peroxide has bactericidal properties, thereby minimizing bacterial resistance.<sup>39 45</sup> Topical antibiotic courses should be limited to 12 weeks' duration when possible.<sup>9 16 46</sup> Finally, combined topical and oral antibiotics should be avoided.<sup>15 47</sup>

**Benzoyl peroxide**

Benzoyl peroxide is a non-antibiotic antimicrobial agent that has bactericidal effects by generating reactive oxygen species within the follicle.<sup>15 32 48 49</sup> It also has weak comedolytic and anti-inflammatory properties.<sup>32</sup> Owing to its bactericidal properties, benzoyl peroxide produces rapid improvement in inflammatory lesions and prevents the development of antibiotic resistance.<sup>15 32 39 45 48-52</sup> Although data on the comparative efficacy and tolerability of benzoyl peroxide and topical retinoid monotherapy are conflicting, most guidelines recommend a mechanistically driven approach, with the addition of benzoyl peroxide mainly when inflammatory lesions are present.<sup>9 10 17</sup> Some studies, including a small double blind randomized trial, show that inflammatory lesions improve more rapidly with benzoyl peroxide than with topical retinoids.<sup>53</sup>

Benzoyl peroxide is available in numerous formulations, in concentrations ranging from 2.5% to 10%,<sup>29</sup> none of which show clear superiority in systematic reviews, although irritation increased with higher concentrations.<sup>27 32 48 52</sup> Irritation typically resolves with continued use. In addition, patients should be warned that benzoyl peroxide may bleach clothing, bedding, and hair.<sup>13 32</sup> Finally, because all retinoids except adapalene are unstable with benzoyl peroxide, these agents should be applied separately.<sup>18 31 32</sup>

**Combination products**

The benefits of combined regimens include complementary mechanisms of action, reduced risk of antibiotic resistance, and improved treatment outcomes.<sup>2 9 10 13 15 17 18 30 47 48</sup> An increasing number of antibiotic-retinoid and antibiotic-benzoyl peroxide combinations are now available. Retinoid-benzoyl peroxide combinations are limited by retinoid instability in the presence of benzoyl peroxide.

The biggest drawback to combined products is cost. Individual generic components are typically less expensive and can be applied simultaneously with equivalent effects.<sup>32 46</sup> Nevertheless, a small investigator blinded randomized controlled trial found that combined products improve patient adherence by simplifying daily regimens.<sup>54</sup> For many clinicians and patients, this improved ease of application and corresponding increase in adherence justifies the cost of combined therapies.

**Other topical treatments**

*Azelaic acid*

Azelaic acid is an alternative to retinoids that has comedolytic, antimicrobial, and anti-inflammatory properties.<sup>9 13 17</sup> This agent has not been approved for acne by the US Food and Drug Administration, although it has been approved in many European countries, so receives greater emphasis in the European literature.<sup>10 55</sup> A small double blind randomized trial demonstrated efficacy of azelaic acid relative to placebo.<sup>56</sup> Studies comparing azelaic acid with other topical agents are limited. Azelaic acid is well tolerated but poses a risk of hypopigmentation in darker skinned patients.<sup>17</sup>

*Salicylic acid*

Salicylic acid is an over-the-counter agent with desquamating and comedolytic properties that is less potent than retinoids.<sup>48</sup> Few studies of salicylic acid exist, although available studies show that it is less effective but better tolerated than other agents.<sup>17 29 48</sup> Salicylic acid may be used when patients cannot tolerate standard agents.

**Systemic agents**

Systemic agents should be considered for patients with moderate to severe acne. These therapies are useful in patients with truncal disease in whom application of topical agents would be difficult.

**Hormonal therapies**

Hormonal therapies are a useful adjunct to treatment in women with moderate to severe acne, especially those who desire oral contraception or in whom traditional therapy has failed.<sup>27</sup> Anecdotal evidence suggests that women with lesions confined to the lower face and jaw are most likely to benefit.<sup>15 57</sup> Hormonal agents are available in two primary forms: combined oral contraceptives, which suppress ovarian androgen production, and androgen receptor blockers, such as cyproterone acetate, spironolactone, and flutamide. In the UK, a combined oral contraceptive containing cyproterone acetate and ethinylestradiol is licensed for the treatment of acne.<sup>13 57 58</sup> These agents decrease androgen mediated effects on the sebaceous follicle.<sup>57</sup> Although hyperandrogenic states such as polycystic ovarian syndrome are associated with acne, most women with acne have normal androgen levels but still benefit from antiandrogen therapy.<sup>57</sup> Full benefit is seen after three to six months of treatment.<sup>15</sup>

A recent Cochrane review confirmed the efficacy of combined oral contraceptives in treating inflammatory and non-inflammatory acne but found few differences in efficacy between the different types, including cyproterone acetate, which is often recommended.<sup>59 60</sup> It is therefore not clear whether formulations containing cyproterone acetate should

**AREAS FOR FUTURE RESEARCH**

Large randomized controlled trials on the treatment of acne are needed  
 Comparative effectiveness research should be prioritized, as cited by the Institute of Medicine<sup>77</sup>  
 Study of the cutaneous microbiome, including disease associations with *Propionibacterium acnes* strains, may improve our understanding of the pathogenesis of acne and open up new therapeutic approaches<sup>78</sup>

be favored, especially because this agent may increase the risk of venous thromboembolism.<sup>27 57 59</sup> Progesterin only contraceptives may worsen acne.<sup>9</sup>

### Oral antibiotics

Systemic antibiotics are indicated for moderate to severe inflammatory acne.<sup>9</sup> Like topical antibiotics, oral antibiotics have antimicrobial and anti-inflammatory effects.<sup>13 39 50</sup> Doxycycline, minocycline, lymecycline, tetracycline, and erythromycin are most commonly used. Few comparative studies exist, although a systematic review of systemic therapy with tetracyclines found no antibiotic to be more effective than another.<sup>17 41 46</sup> Although minocycline was previously favored by clinicians, a recent Cochrane review found no clear evidence of superiority.<sup>61 62</sup> Given the lack of comparative data, antibiotic selection may be driven by side effect profiles and patterns of *P acnes* resistance. Tetracyclines must be avoided in pregnant women and children given the associated risk of tooth discoloration. Women of childbearing age should be advised to use contraception when taking these agents. Doxycycline causes photosensitivity. In rare cases minocycline leads to skin hyperpigmentation and drug induced systemic lupus erythematosus. Limecycline has gained popularity in Europe but is not available in the US.<sup>63</sup> Increasing *P acnes* resistance has decreased reliance on erythromycin and tetracycline.<sup>11 42 49 50</sup>

As with topical antibiotics, oral antibiotics should be combined with other agents to minimize the development of

bacterial resistance and improve treatment efficacy. Always use oral antibiotics in conjunction with a topical retinoid or benzoyl peroxide<sup>16 50</sup>—several small to moderate sized randomized controlled trials have shown that this increases efficacy.<sup>64-66</sup> Assess treatment response at six to eight weeks, at which point a decision to continue or change antibiotics may be made.<sup>50</sup> When possible, limit antibiotic courses to 12 weeks' duration.<sup>2 16 46</sup>

### Isotretinoin

Isotretinoin is remarkably efficacious in the treatment of severe acne, as well as treatment resistant moderate disease, and is now the first line treatment in such cases.<sup>10 13</sup> Isotretinoin is thought to target all four components involved in the development of acne by normalizing follicular desquamation, decreasing sebum secretion, inhibiting the growth of *P acnes*, and exerting anti-inflammatory effects.<sup>13 31 49</sup> Given these broad effects and the potential for adjunctive therapy to compound adverse effects, isotretinoin is prescribed as monotherapy.

Patients typically complete a 16-24 week course of isotretinoin, taking 0.5-1 mg per kg per day to target a cumulative dose of 120-150 mg per kg.<sup>11 16 49</sup> The dose is slowly increased as tolerated. Effects are not usually seen for the first one or two months.<sup>67</sup> Meta-analyses show that at least half of patients are permanently cured after a single course, and only 20% of patients require repeat treatment.<sup>15 17 31 49 68 69</sup> Relapse is most common in younger patients, in women with hormonally driven acne, and when goal cumulative dosing is not achieved.<sup>31 57 70 71</sup>

Use of oral isotretinoin is tightly regulated because of its well known teratogenic effects and is available through specialist care only in many countries.<sup>42</sup> Female patients must demonstrate a negative pregnancy test and use contraception.<sup>49</sup> Although charged with having detrimental psychological effects, there is no clear evidence that isotretinoin leads to depression or suicidality.<sup>72-74</sup> Other adverse reactions include chapped skin, dry eyes, epistaxis, myalgias, and alterations in serum lipid and transaminase concentrations, most of which resolve after treatment is stopped.<sup>11 13 31 49</sup>

### What are the consequences of acne?

Although many people dismiss acne vulgaris as an inconsequential disease of adolescence, it has clear long lasting psychosocial and physical effects. Many studies have shown an association between acne and depression and anxiety, independent of disease severity.<sup>7 75</sup> Psychological effects improve with treatment.<sup>76</sup> Furthermore, acne may cause permanent scarring that is difficult to correct. Finally, because of its frequency and chronicity, the economic burden of acne is substantial, with associated expenditure in the US alone exceeding \$2.5bn (£1.64bn; €1.93bn) annually.<sup>20</sup> To reduce these effects, patients with acne should receive early, aggressive, mechanistically driven therapy.

Contributors: Both authors had full access to the content of this review and are guarantors. ALD searched the literature, compiled the references, and drafted the manuscript. RPD critically revised the manuscript for intellectual content.

Competing interests: None declared.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent obtained.

References are in the version on bmj.com.

### ADDITIONAL EDUCATIONAL RESOURCES

#### Resources for healthcare professionals

American Academy of Dermatology: Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC, et al. Guidelines of care for acne vulgaris management. *J Am Acad Dermatol* 2007;56:651-63

European Dermatology Forum: 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

Global Alliance to Improve Outcomes in Acne: Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, 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

National Institute of Health and Care Excellence ([www.cks.nhs.uk/acne\\_vulgaris](http://www.cks.nhs.uk/acne_vulgaris))—Clinical knowledge summary on acne vulgaris

#### Resources for patients

American Academy of Dermatology ([www.aad.org/skin-conditions/dermatology-a-to-z/acne](http://www.aad.org/skin-conditions/dermatology-a-to-z/acne))—Basic patient information regarding acne treatment with particular emphasis on adult acne

British Association of Dermatologists ([www.bad.org.uk/site/793/default.aspx](http://www.bad.org.uk/site/793/default.aspx))—General overview of acne treatment

National Institute of Health and Care Excellence ([www.cks.nhs.uk/acne\\_vulgaris](http://www.cks.nhs.uk/acne_vulgaris))—Clinical knowledge summary on acne vulgaris

UpToDate Patient Information ([www.uptodate.com/contents/acne-beyond-the-basics](http://www.uptodate.com/contents/acne-beyond-the-basics))—Patient oriented guide to the pathophysiology and treatment of acne