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Guidelines of care for acne vulgaris management

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Disclaimer: Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient.
INTRODUCTION/METHODOLOGY

A work group of recognized experts was convened to determine the audience for the guidelines, define the scope of the guidelines, and identify nine clinical questions to structure the primary issues in diagnosis and management. Work group members were asked to complete a disclosure of commercial support, and this information will be in the acne technical report available on www.aad.org.

An evidence-based model was used and some evidence was obtained by a vendor using a search of MEDLINE and EMBASE databases spanning the years 1970 through 2006. Only English-language publications were reviewed.

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy (SORT) developed by editors of the US family medicine and primary care journals (ie, American Family Physician, Family Medicine, Journal of Family Practice, and BMJ-USA). This strategy was supported by a decision of the Clinical Guidelines Task Force in 2005 with some minor modifications for a consistent approach to rating the strength of the evidence of scientific studies.1 Evidence was graded using a three-point scale based on the quality of methodology as follows:

- I. Good quality patient-oriented evidence.
- II. Limited quality patient-oriented evidence.
- III. Other evidence including consensus guidelines, extrapolations from bench research, opinion, or case studies.

Clinical recommendations were developed on the basis of the best available evidence presented in the guidelines and explained further in the technical report. These are ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence.
B. Recommendation based on inconsistent or limited quality patient-oriented evidence.
C. Recommendation based on consensus, opinion, or case studies.

These guidelines have been developed in accordance with the American Academy of Dermatology/American Academy of Dermatology Association “Administrative Regulations for Evidence-Based Clinical Practice Guidelines,” which include the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.

Scope

These guidelines address the management of adolescent and adult patients presenting with acne but not the consequences of disease, including the scarring, post-inflammatory erythema, or post-inflammatory hyperpigmentation. The topic of light and laser therapy will be the subject of another guideline.

Definitions

Acne vulgaris is a chronic inflammatory dermatosis which is notable for open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules, or nodules.

Issues

The task force identified the following clinical issues relevant to the management of acne: grading and classification; the role of microbiologic and endocrine testing; and the efficacy and safety of various treatments, such as topical agents, systemic antibacterial agents, hormonal agents, isotretinoin, miscellaneous therapies, complementary/alternative therapies, and dietary restriction.

I. SYSTEMS FOR THE GRADING AND CLASSIFICATION OF ACNE

Table I shows the recommendations for a grading and classification system.

Recommendation

- Clinicians may find it helpful to use a consistent classification/grading scale (encompassing the numbers and types of acne lesions as well as disease severity) to facilitate therapeutic decisions and assess response to treatment.

DISCUSSION

The rating of disease severity is useful for the initial evaluation and management of acne, to aid in the selection of appropriate therapeutic agents, and to evaluate response to treatment.2,3 Several systems for grading acne exist; most employ lesion counting combined with some type of global assessment of severity (eg, mild, moderate, severe) that represents a synthesis of the number, size, and extent of lesions. However, there is no consensus on a single or best grading or classification system.2-15

II. MICROBIOLOGIC AND ENDOCRINOLOGIC TESTING

Microbiologic testing

Table II shows the recommendations for microbiologic testing.

Recommendations

- Routine microbiologic testing is unnecessary in the evaluation and management of patients with acne.
Those who exhibit acne-like lesions suggestive of gram-negative folliculitis may benefit from microbiologic testing.

**DISCUSSION**

The prevalent bacterium implicated in the clinical course of acne is *Propionibacterium acnes* (*P. acnes*), a gram-positive anaerobe that normally inhabits the skin and is implicated in the inflammatory phase of acne.

Gram-negative folliculitis is typically characterized by pustules and/or nodules most commonly located in the perioral and nasal areas. Gram-negative folliculitis is caused by a variety of bacteria and is unresponsive to conventional antibiotic therapy for acne. Bacterial cultures, including antibacterial sensitivities, are usually of value in establishing the diagnosis and in determining therapy.16-19

**Endocrinologic testing**

Table III shows the recommendations for endocrinologic testing.

**Recommendation**

- Routine endocrinologic evaluation (eg, for androgen excess) is not indicated for the majority of patients with acne. Laboratory evaluation is indicated for patients who have acne and additional signs of androgen excess. In young children this may be manifested by body odor, axillary or pubic hair, and clitoromegaly. Adult women with symptoms of hyperandrogenism may present with recalcitrant or late-onset acne, infrequent menses, hirsutism, male or female pattern alopecia, infertility, polycystic ovaries, clitoromegaly, acanthosis nigricans, and truncal obesity.20-24

**DISCUSSION**

Although androgens play an important role in the pathogenesis of acne, most patients have normal hormone levels. Presently, there is little evidence from peer-reviewed literature indicating that routine endocrinologic testing has clinical value in the evaluation of patients with acne. Patients whose history or physical examination suggests hyperandrogenism may, however, benefit from such testing. In prepubertal children, the signs include acne, early-onset body odor, axillary or pubic hair, accelerated growth, advanced bone age, and genital maturation. After puberty, common virilizing signs and symptoms are infrequent menses, hirsutism, male or female pattern alopecia, infertility, polycystic ovaries, clitoromegaly, acanthosis nigricans, and truncal obesity.20-24 In prepubertal children, a hand film for bone age is a practical screen prior to specific hormonal testing. Increased awareness of clinical signs of androgen excess will help identify those patients who may benefit from further evaluation and treatment by an endocrinologist or gynecologic endocrinologist. It is the opinion of the experts that the following laboratory tests may be helpful: free testosterone, dehydroepiandrosterone sulfate, leutinizing hormone, and follicule-stimulating hormone.

**III. TOPICAL THERAPY**

Recommendations for topical therapy are shown in Table IV.

**Recommendations**

- Topical therapy is a standard of care in acne treatment.
- Topical retinoids are important in acne treatment.
- Benzoyl peroxide and combinations with erythromycin or clindamycin are effective acne treatments.
- Topical antibiotics (eg, erythromycin and clindamycin) are effective acne treatments. However, the use of these agents alone can be associated with the development of bacterial resistance.
• Salicylic acid is moderately effective in the treatment of acne.
• Azelaic acid has been shown to be effective in clinical trials, but its clinical use, compared to other agents, has limited efficacy according to experts.
• Data from peer-reviewed literature regarding the efficacy of sulfur, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc are limited.
• Employing multiple topical agents that affect different aspects of acne pathogenesis can be useful. However, it is the opinion of the work group that such agents not be applied simultaneously unless they are known to be compatible.

DISCUSSION

Topical retinoids
The effectiveness of topical retinoids in the treatment of acne is well documented.25-41 These agents act to reduce obstruction within the follicle and therefore are useful in the management of both comedonal and inflammatory acne. There is no consensus about the relative efficacy of currently available topical retinoids (tretinoin, adapalene, tazarotene, and isotretinoin). The concentration and/or vehicle of any particular retinoid may impact tolerability.34,35 Topical isotretinoin is not currently available in the United States.

Benzoyl peroxide
Benzoyl peroxide is a bactericidal agent that has proven effective in the treatment of acne. It is available in a variety of concentrations and vehicles; however, there is insufficient evidence to evaluate and compare the efficacy of these different formulations. It has the ability to prevent or eliminate the development of P. acnes resistance.42-51 Because of concerns of resistance, it is often used in the management of patients treated with oral or topical antibiotics.

Topical antibiotics
The value of topical antibiotics in the treatment of acne has been investigated in many clinical trials. Both erythromycin52-58 and clindamycin59-66 have been demonstrated to be effective and are well tolerated. Decreased sensitivity of P. acnes to these antibiotics can limit the use of either drug as a single therapeutic agent.58,61

Combinations: Retinoids, benzoyl peroxide, and topical antibiotics
A combination of topical retinoids and topical erythromycin or clindamycin is more effective than either agent used alone.67-71 Combining erythromycin or clindamycin with benzoyl peroxide eliminates or reduces bacterial resistance and enhances efficacy. The combinations are more effective than either of the individual components alone.72-75

Salicylic acid
Salicylic acid has been used for many years for the treatment of acne, although few well-designed trials of its safety and efficacy exist. Its comedolytic properties are considered less potent than topical retinoids. It often is used when patients cannot tolerate a topical retinoid because of skin irritation.76

Other topical agents
Azelaic acid has been reported to possess comedolytic and antibacterial properties. Data from clinical trials indicate that it is effective.77-79 Although sulfur and resorcinol have been used for many years in the treatment of acne, evidence from peer-reviewed literature supporting their efficacy is lacking.80 Aluminum chloride possesses antibacterial activity and, therefore, has been investigated in the treatment acne. Of two studies in the peer-reviewed literature, one found benefit81 and one did not.82 Topical zinc alone is ineffective.83-85 There is some evidence to suggest efficacy for sodium sulfacetamide.86-88

IV. SYSTEMIC ANTIBIOTICS
The recommendations of systemic antibiotics are shown in Table V.

Recommendations
• Systemic antibiotics are a standard of care in the management of moderate and severe acne and treatment-resistant forms of inflammatory acne.
• Doxycycline and minocycline are more effective than tetracycline, and there is evidence that minocycline is superior to doxycycline in reducing P. acnes.
• Although erythromycin is effective, use should be limited to those who cannot use the tetracyclines (ie, pregnant women or children under 8 years of age because of the potential for damage to the skeleton or teeth). The development of bacterial resistance is also common during erythromycin therapy.
• Trimethoprim-sulfamethoxazole and trimethoprim alone are also effective in instances where other antibiotics cannot be used.
• Bacterial resistance to antibiotics is an increasing problem.
• The incidence of significant adverse effects with antibiotic use is low. However, adverse effect profiles may be helpful for each systemic antibiotic used in the treatment of acne.
DISCUSSION

Antibiotics have been widely used for many years in the management of acne. There is evidence to support the use of tetracycline, doxycycline, minocycline, erythromycin, trimethoprim-sulfamethoxazole, trimethoprim, and azithromycin. Studies do not exist for the use of ampicillin, amoxicillin, or cephalaxin. However, any antibiotic which can reduce the *P. acnes* population in vivo and interfere with the organism’s ability to generate inflammatory agents should be effective. It is the opinion of the expert panel that while published data are conflicting, minocycline and doxycycline are more effective than tetracycline.

A major problem affecting antibiotic therapy of acne has been bacterial resistance, which has been increasing. For this reason, it is the opinion of the work group that patients with less severe forms of acne should not be treated with oral antibiotics, and where possible the duration of such therapy should be limited. Resistance has been seen with all antibiotics, but is most common with erythromycin.

The use of oral antibiotics for the treatment of acne may be associated with adverse effects. Vaginal candidiasis may complicate the use of all oral antibiotics, and where possible the duration of such therapy should be limited. Resistance has been seen with all antibiotics, but is most common with erythromycin.

The use of oral antibiotics for the treatment of acne may be associated with adverse effects. Vaginal candidiasis may complicate the use of all oral antibiotics.

Spironolactone can be associated with photosensitivity. Minocycline has been associated with pigment deposition in the skin, mucous membranes and teeth particularly among patients receiving long-term therapy and/or higher doses of the medication. Pigmentation occurs most often in acne scars, anterior shins, and mucous membranes.

V. HORMONAL AGENTS

Hormonal agent recommendations are shown in Table VI.

Recommendations

- Oral antiandrogens, such as spironolactone and cyproterone acetate, can be useful in the treatment of acne. While flutamide can be effective, hepatic toxicity limits its use. There is no evidence to support the use of finasteride.
- There are limited data to support the effectiveness of oral corticosteroids in the treatment of acne. There is a consensus of expert opinion that oral corticosteroid therapy is of temporary benefit in patients who have severe inflammatory acne.
- In patients who have well-documented adrenal hyperandrogenism, low-dose oral corticosteroids may be useful in treatment of acne.

Oral contraceptives

There are clinical trials of estrogen-containing contraceptive agents for the treatment of acne. Those currently approved by the US Food and Drug Administration (FDA) for the management of acne contain norgestimate with ethinyl estradiol (Ortho Tri-cyclen; Ortho-MacNeil Pharmaceutical, Inc, Raritan, NJ) and norethindrone acetate with ethinyl estradiol (Estrostep; Warner Chilcott, Rockaway, NJ). There is good evidence and consensus opinion that other estrogen-containing oral contraceptives are also equally effective. The effect on acne of other estrogen-containing contraceptives (eg, transdermal patches, vaginal rings) has not been studied.

Spironolactone

Spironolactone is an anti-androgen that exerts its effects by blocking androgen receptors at higher doses. Dosages of 50 mg to 200 mg have been shown to be effective in acne. Spironolactone may cause hyperkalemia, particularly when higher doses are prescribed or when there is cardiac or renal compromise. It occasionally causes menstrual irregularity.

Cypoterone acetate

Cypoterone combined with ethinyl estradiol (in the form of an oral contraceptive) has been found to...
be effective in the treatment of acne in females. Higher doses have been found to be more effective than lower doses. Cyproterone/estrogen-containing oral contraceptives are not approved for use in the United States.

Flutamide

Flutamide, a non-steroidal antiandrogen approved for the management of prostatic hypertrophy or cancer and hirsutism, has had some success in the management of acne, but its use is limited because of the potential of hepatic failure.

Other antiandrogens

Finasteride and other compounds with possible antiandrogenic effects (eg, cimetidine and ketoconazole) have not been reported to be effective in acne.

Oral corticosteroids

Oral corticosteroids may have two modes of activity in the treatment of acne. One study demonstrated that low dose corticosteroids suppress adrenal activity in patients who have proven adrenal hyperactivity. Expert opinion is that short-courses of higher dose oral corticosteroids may be beneficial in patients with highly inflammatory disease.

VI. ISOTRETINOIN

Isotretinoin recommendations are shown in Table VII.

Recommendations

- Oral isotretinoin is approved for the treatment of severe recalcitrant nodular acne.
- It is the unanimous opinion of the acne workgroup that oral isotretinoin is also useful for the management of lesser degrees of acne that are treatment-resistant or for the management of acne that is producing either physical or psychological scarring.
- Oral isotretinoin is a potent teratogen. Because of its teratogenicity and the potential for many other adverse effects, this drug should be prescribed only by those physicians knowledgeable in its appropriate administration and monitoring.
- Female patients of child-bearing potential must only be treated with oral isotretinoin if they are participating in the approved pregnancy prevention and management program (iPLEDGE; see below).
- Mood disorders, depression, suicidal ideation, and suicides have been reported in patients taking this drug. However, a causal relationship has not been established.

DISCUSSION

Indications

The approved indication for the use of oral isotretinoin has remained severe nodular treatment-resistant acne since the drug was introduced more than 20 years ago. However, it is the opinion of the expert work group that this drug is also indicated for all cases of acne that are either treatment-resistant or producing physical or psychological scarring.

Dosage

The approved dosage is 0.5 to 2.0 mg/kg/day. The drug is usually given over a 20-week course. Drug absorption is greater when the drug is taken with food. The acne expert work group feels strongly that initial flaring can be minimized with a beginning dose of 0.5 mg/kg/day or less. Alternatively, lower doses can be used for longer time periods, with a total cumulative dose of 120 to 150 mg/kg. In patients who have severely inflamed acne, even greater initial reduction of dose may be required. In the most severe cases of acne, consideration of pre-treatment with oral corticosteroids may also be appropriate.

Adverse effects

Isotretinoin, a vitamin A derivative, interacts with many of the biologic systems of the body, and consequently has a significant pattern of adverse effects. The pattern is similar to that seen in hypervitaminosis A. Side effects include those of the mucocutaneous, musculoskeletal, and ophthalmic systems, as well as headaches and central nervous system effects. Most of the adverse effects are temporary and resolve after the drug is discontinued.

While hyperostosis, premature epiphyseal closure, and bone demineralization have been observed with prolonged use of higher dose retinoids, in the usual course of acne treatment these findings have not been identified. Therefore it is the unanimous opinion of the acne work group that routine screening for these issues is not required. Laboratory monitoring during therapy should include triglycerides, cholesterol, transaminase, and complete blood counts.

Changes in mood, suicidal ideation, and suicide have been reported sporadically in patients taking...
Table VIII. Recommendations for miscellaneous therapies

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<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Level of evidence</th>
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<td>C</td>
<td>III</td>
<td>168, 169</td>
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<tr>
<td>Chemical peels</td>
<td>C</td>
<td>III</td>
<td>170-172</td>
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<tr>
<td>Comedo removal</td>
<td>C</td>
<td>III</td>
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isotretinoin. While these events have been seen, a causal relationship has not been established. Nonetheless, there are instances in which withdrawal of isotretinoin has resulted in improved mood and reintroduction of isotretinoin has resulted in the return of mood changes. The symptoms mentioned are quite common in adolescents and young adults, the age range of patients who are likely to receive isotretinoin. Treatment of severe acne with isotretinoin is often associated with mood improvement. There is epidemiologic evidence that the incidence of these events is less in isotretinoin-treated patients than in an age-matched general population. There is also evidence that the risk of depressed mood is no greater during isotretinoin therapy than during therapy of an age-matched acne group treated with conservative therapy. Nonetheless, patients must be made aware of this possibility and treating physicians should monitor patients for psychiatric adverse effects.159-165

Some patients experience a relapse of acne after the first course of treatment with isotretinoin. The panel feels relapses are more common in younger adults or when lower doses are used.147-149,151,166,167

iPLEDGE

Because of the teratogenic effects of isotretinoin on the fetus, the FDA and the manufacturers have approved a new risk management program for isotretinoin.154,155 Prescribers, patients, pharmacies, drug wholesalers, and manufacturers in the United States are required to register and comply with the iPLEDGE program. This program requires mandatory registration of all patients receiving this drug. Detailed information can be found on the iPLEDGE web site (www.ipledgeprogram.com).

VII. MISCELLANEOUS THERAPY

Recommendations for miscellaneous therapies are shown in Table VIII.

Recommendations

- Intralesional corticosteroid injections are effective in the treatment of individual acne nodules.
- There is limited evidence regarding the benefit of physical modalities including glycolic acid peels and salicylic acid peels.

Table IX. Recommendations for complementary therapies

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<th>Strength of recommendation</th>
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<td>II</td>
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<tr>
<td>Psychological approaches</td>
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<td>177</td>
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<tr>
<td>Hypnosis/biofeedback</td>
<td>B</td>
<td>II</td>
<td>178</td>
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DISCUSSION

Intralesional steroids

In the opinion of experts, the effect of intralesional injection with corticosteroids is a well established and recognized treatment for large inflammatory lesions. It has been found that patients receiving intralesional steroids for the treatment of cystic acne improved.168 Systemic absorption of steroids may occur. Adrenal suppression was observed in one study.169 The injection of intralesional steroids may be associated with local atrophy. Lowering the concentration and/or volume of steroid utilized may minimize these complications.

Chemical peels

Both glycolic acid-based and salicylic acid-based peeling preparations have been used in the treatment of acne. There is very little evidence from clinical trials published in the peer-reviewed literature supporting the efficacy of peeling regimens.170-172 Further research on the use of peeling in the treatment of acne needs to be conducted in order to establish best practices for this modality.

Comedo removal

There is limited evidence published in peer-reviewed medical literature that addresses the efficacy of comedo removal for the treatment of acne, despite its long-standing clinical use.173 It is, however, the opinion of the work group that comedo removal may be helpful in the management of comedones resistant to other therapies. Also, while it cannot affect the clinical course of the disease, it can improve the patient’s appearance, which may positively impact compliance with the treatment program.

VIII. COMPLEMENTARY THERAPY

Complementary therapy recommendations are shown in Table IX.
Recommendation
- Herbal and alternative therapies have been used to treat acne. Although these products appear to be well tolerated, very limited data exist regarding the safety and efficacy of these agents.

DISCUSSION
A single clinical trial has demonstrated that topical tea tree oil is effective for the treatment of acne, although the onset of action is slower compared to other topical treatments.174 Other herbal agents, such as topical and oral ayurvedic compounds, have been reported to have value in the treatment of acne.175,176

Psychological approaches/hypnosis/biofeedback
The psychological effects of acne may be profound, and it is the unanimous opinion of the expert workgroup that effective acne treatment can improve the emotional outlook of patients. There is weak evidence of the possible benefit of biofeedback-assisted relaxation and cognitive imagery.177,178

IX. DIETARY RESTRICTION
Recommended dietary restrictions are shown in Table X.

Recommendation
- Dietary restriction (either specific foods or food classes) has not been demonstrated to be of benefit in the treatment of acne.

DISCUSSION
There are few clinical studies available in the peer-reviewed literature that directly evaluate the effectiveness of dietary restriction or the consumption of specific foods or food groups to improve acne. Studies addressing the potential for particular foods to exacerbate acne have been conducted.179,180 These studies fail to support a link between the consumption of chocolate or sugar and acne. Thus, no evidence exists on the role of diet in acne.

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