



Newest Guidelines for the Treatment of Acne

Abstract

This article summarizes key statements from the 2009 Global Alliance to Improve Outcomes in Acne Group's therapeutic guidelines, published as a supplement in the Journal of the American Academy of Dermatology (JAAD). It offers an algorithm for acne treatment, as well as addresses important statements from the committee on acne pathophysiology, epidemiology, and the latest research findings, as they pertain to the guidelines.

Keywords: *acne, treatment guidelines, adherence, antibiotic resistance, maintenance*

The Global Alliance to Improve Outcomes in Acne Group ("Global Alliance") is an international group of dermatologists with clinical and research expertise in acne vulgaris. The group was formed 10 years ago with arm's-length support from Galderma International. Over 20 dermatologists from North America, Europe, Asia, and Australia have served on this committee. The group has conducted research studies and published widely. Initiating programs to improve consumer and practitioner knowledge has been a priority. As an Alliance member, I have had the opportunity to work on the guidelines and especially contribute to the Group's efforts to define acne as a chronic disease.

The first consensus guidelines were published in 2003 in JAAD and were very well received as an evidence-based and thoughtful document.¹ In the 2009 guidelines updated information on pathogenesis, mechanism of action of therapies, and clinical results are presented.² The update offers new insights into the prevention and management of scarring, and reflects the shift of thinking of acne vulgaris as a chronic disease rather than an acute condition. This approach is helpful in understanding short- and long-term goals and strategies for

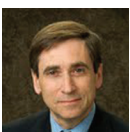
success. However, such a shift highlights the need for patient education—and the need, in some cases, to educate their physicians. The Alliance holds that dermatologists should be at the forefront in educating other clinicians that acne has characteristics that have traditionally defined chronicity (frequent relapse/recurrence, prolonged course, severe psychosocial impact, etc.).

The Global Alliance has long been committed to reducing the overuse of antimicrobial therapies, especially as single agents. Despite many extensive educational programs this is still a widespread practice and antimicrobial resistance is still on the rise. The 2009 update is quite detailed in this area.

Of course, a key area of interest for members of the Alliance is offering guidelines for dermatologists and other clinicians on choosing the best treatments, early in the course of the disease, with the hope of providing the best long-term outcomes.

Acne Pathophysiology

Acne vulgaris is very common and can be misconstrued as a "rite of passage." But the psychological impact, even of low-severity acne, can be devastating.



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Treatments are aimed at treating active disease and just as importantly at preventing new disease. Essential to an appropriate understanding of acne as a chronic disease is a clear sense of acne pathophysiology, and the update summarizes the latest research findings (Table 1).

The primary lesion in acne vulgaris is the microcomedo, a “plugged” follicular opening that is only visible microscopically and is the precursor to visible comedones and inflammatory papules (Figure 1). Acne is partially driven by hormonal influences and inflammatory pathways, but most topical treatments target the comedo itself with comedolytic agents. Antimicrobial agents are not comedolytic, but retinoids and benzoyl peroxide are.

The Latest Guidelines

The key areas of update are proven strategies to reduce antimicrobial resistance, and the use of lasers, other light sources and photodynamic therapy; further, the guidelines explore the increased role for combination therapies. Clinicians will find in this updated document not only summary statements and recommendations but also indication of the level of evidence that currently supports each finding.

Retinoids, Benzoyl Peroxide, Antibiotics, and Combination Therapies

Retinoids have an increasingly relevant role in the acute and maintenance therapy of acne. Combination strategies, either with fixed combinations or two or more products used simultaneously, have worked best. This has been a key area of evolution since the 2003 Global Alliance Recommendations. The newest guidelines are clear: “Combination retinoid-based [topical] therapy is first line therapy for acne.” This is based on clinical trials with over 16,000 total subject participants in studies of top-grade (Level I) evidence quality.

Interestingly, there is evidence for faster resolution and better results with the topical retinoid adapalene and oral tetracyclines compared to the products alone (Level I evidence) and for tretinoin and tazarotene in combination with oral antibiotics (Level III evidence).

BECAUSE OF THEIR COMEDOLYTIC AND ANTI-INFLAMMATORY PROPERTIES, TOPICAL RETINOIDS ARE A CORNERSTONE OF THERAPY.

Table 1: What Is New in Acne Pathophysiology

- Inflammatory events have been found to precede hyperkeratinization
- *P. acnes* contributes to inflammation via activation of toll-like receptor (TLR) on the membranes of inflammatory cells
- Peroxisome proliferator-activated receptors partly regulate sebum production
- The sebaceous gland is a neuroendocrine inflammatory organ that likely coordinates and executes a local response to stress and normal functions
- Androgens have influence on follicular keratinocytes
- Oxidized lipids in sebum can stimulate production of inflammatory mediators
- Matrix metalloproteinases (MMPs) occur in sebum and diminish with treatment-related resolution of acne lesions

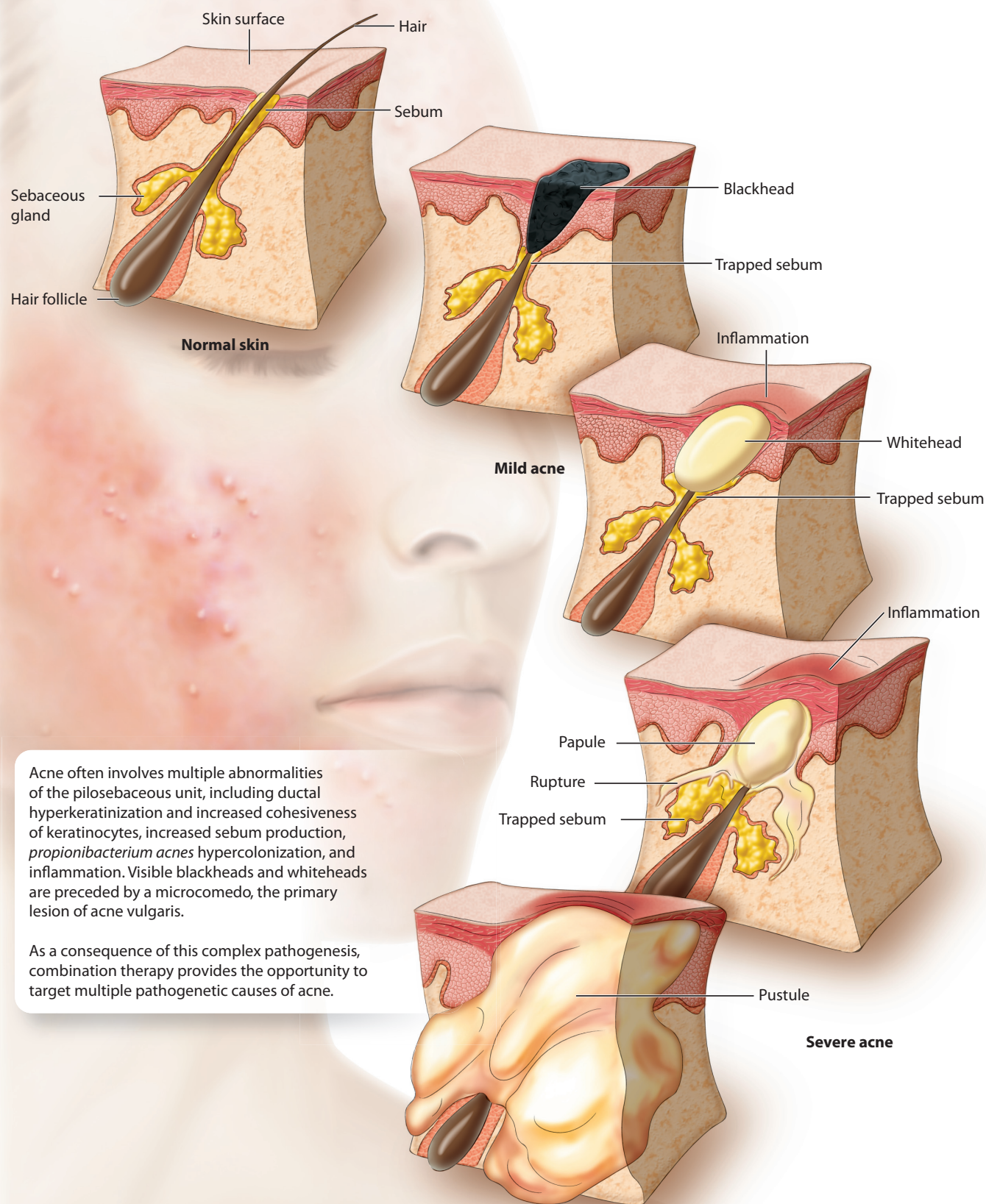
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Key Point

Dermatologists should be actively contributing to educating other clinicians that acne is a chronic disease.

Figure 1: Pathogenesis of Acne Vulgaris



There is a clear statement against the use of antibiotics, topically or orally as monotherapy. There is a risk when antibiotics are used in combination with retinoids over an extended period. However, the concomitant use of the nonantibiotic antimicrobial agent benzoyl peroxide (BPO) can reduce the risk of emergent resistant organisms (Level V evidence). Combination therapy is easier when multiple medications are in a single product. Existing retinoid-antibiotic combinations are important but often underutilized. Newer retinoid (e.g., adapalene)-BPO products have an advantage, especially in the long-term view, of removing antibiotics from the regimen and reducing the risk of resistance.

Ultimately, with a well-chosen and well-tolerated therapy all of the pathogenic contributors of the microcomedo that lead to acne can be controlled.

Light Therapies for Acne

Light in the form of laser, intense pulse light, and photodynamic therapy may work in specific situations. The problems with studies of new technologies are that the current equipment may not be representative of what was reported, and practitioner specifics can have a large impact on outcomes. The Alliance concluded that existing studies were of variable quality. Those available infrequently compared light-based treatments with well-validated pharmaceutical treatments, and little information is available as to long-term effects of photodynamic therapies.

The Alliance observed that early data suggest that light treatments may have benefit as an adjunct to medical therapy or be suited for patients who decline or cannot tolerate available medical therapies. Clinical data on these therapies remain emergent, however, and the Alliance concluded that current evidence is insufficiently robust to recommend any device be used as monotherapy in treating acne vulgaris (Level V evidence). Nevertheless, light therapies are currently being used by some patients with

success, and anecdotal evidence suggests that dramatic results can be obtained in the short and intermediate term for some patients.

Scarring

There are many types of acne scars, from pigmentary changes to keloids, and a myriad of acne scar treatments. The primary consensus statement from the Alliance is that early and appropriate treatment, continued for as long as necessary, is the best approach to mitigating scarring.

A list of validated treatment options includes chemical peels, microdermabrasion, laser (ablative and nonablative; fractional), surgery with punch excision and elevation, or subcision, and fillers. Combinations of these and multiple treatments are commonly used. A detailed review of the section of the guidelines concerning scarring is beyond the scope of this review, but readers interested in currently available treatments for cosmetic improvement of acne scarring should consult the document.

Adherence to a Therapeutic Plan

Even though acne has a tremendous impact on decreasing quality of life, many patients do not adhere to daily treatment regimens. Many studies now help us recognize the patients who will follow the plan and suggest helpful techniques to improve compliance and hence improve outcomes. The 2009 update offers several suggestions for improving patient adherence to therapeutic plans (Table 2).

For example, attributes of the patient, such as female sex, and older age, are associated with increased adherence. Attributes of the treatment that favour better adherence are combinations, once-daily regimens, gel formulation, and oral therapies such as isotretinoin. Explanations of the reasons for therapy are not often as

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Table 2: Global Alliance Recommendations: Improving Treatment Adherence

- Focus on counselling and education, whether done directly by the physician or other health professionals
- Improve outcomes by showing patient how much medication to use and how it is applied (e.g., applying to entire face rather than spot-treating)
- Address reasons why patient does not correctly follow or complete treatments
- Assess quality of life; it is correlated with treatment outcomes
- Evaluate the likelihood of psychiatric morbidity
- Consider using medication reminders (e.g., text messages), self-monitoring with diaries, support groups, telephone follow-up
- Use available resources and educational tools



Key Point

A combination of a topical retinoid plus an anti-microbial agent is first-line therapy for most patients with acne (a finding based on clinical trials with over 16,000 total subject participants in studies of Level I evidence quality), as it targets multiple pathogenic features and both inflammatory and noninflammatory acne lesions.

impactful as frequent visits to the dermatologist.

Without a strategy for improving adherence there is a great chance of treatment failure. This should be part of every plan in both the acute and maintenance phases of care. Even early success can disappoint when patients stop treatment and acne lesions recur.

Treatment Algorithm

The original 2003 Global Alliance algorithm has been translated into many languages and adapted for the variety of product availability around the world. The 2009 version is slightly condensed and more universal than the original (Figure 2).

The options for treatment are based on the evidence and patient specifics. Different stages or severity of acne require different options. Women may require

Figure 2: Global Alliance Acne Treatment Algorithm

Acne Severity	MILD		MODERATE		SEVERE
	Comedonal	Mixed and Papular/pustular	Mixed and Papular/pustular	Nodular ⁽²⁾	Nodular/Conglobate
1st Choice	Topical Retinoid	Topical Retinoid + Topical Antimicrobial	Oral Antibiotic + Topical Retinoid +/- BPO	Oral Antibiotic + Topical Retinoid + BPO	Oral Isotretinoin ⁽²⁾
Alternatives ⁽¹⁾	Alt. Topical Retinoid or Azelaic acid* or Salicylic acid	Alt. Topical Retinoid Antimicrobial Agent + Alt. Topical Retinoid or Azelaic Acid*	Alt. Oral Antibiotic + Alt. Topical Retinoid +/- BPO	Oral Isotretinoin or Alt. Oral Antibiotic + Alt. Topical Retinoid	High Dose Oral Antibiotic + Topical Retinoid + BPO
Alternatives for Females ^(1,4)	See 1st Choice	See 1st Choice	Oral Antiandrogen + Topical Retinoid/ Azelaic Acid* +/- Topical Antimicrobial	Oral Antiandrogen ⁽³⁾ + Topical Retinoid/ +/- Oral Antibiotic +/- Alt. Antimicrobial	High Dose Oral Antiandrogen ⁽³⁾ + Topical Retinoid +/- Alt. Topical Antimicrobial
Maintenance Therapy	Topical Retinoid		Topical Retinoid +/- BPO		

1. Consider physical removal of comedones. 2. With small nodules (<0.5cm). 3. Second course in case of relapse.

4. For pregnancy, options are limited. 5. For full discussion see Gollnick H. et al. MAD 2003;49 (Suppl):1-37.

*Note: Azelaic acid is not approved for the treatment of acne in Canada.

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SUMMARY OF KEY POINTS

Dermatologists should be actively contributing to educating other clinicians that acne is a chronic disease.

Despite many extensive educational programs, the committee sees an ongoing need to urgently reduce the use of antimicrobial therapies, especially as single agents.

A combination of a topical retinoid plus an antimicrobial agent is first-line therapy for most patients with acne (a finding based on clinical trials with over 16,000 total subject participants in studies of Level I evidence quality), as it targets multiple pathogenic features and both inflammatory and noninflammatory acne lesions.

It is advisable to see patients on maintenance therapy for follow-up—attempt at least two office visits per year, and more if there is an increase in flares.

a different approach from men, but the fundamental basics are universal. Combination topical therapies that minimize exposure to antibiotics will provide the best outcomes overall and reduce risks.

Conclusion

Our understanding of the pathogenesis of acne has continued to expand, and our treatment options have also increased. But the basic message is simple: Our patients see us because they want treatment; they want to have clear skin. The evidence supports combinations that contain retinoids as first-line treatment. However, we must always be enhancing our strategies for improving adherence to therapy. Our attitude to the treatment of acne should be one of support and hope. Regimens can be simple and clear, but until we refine our clinical techniques we will not achieve optimal outcomes.

The work of the Global Alliance has been inspiring. The breadth of literature review is clear in the 2009 supplement,

and hopefully the group members can continue their work and share their findings on newer treatments and improved strategies. Ideally, practitioners will acquaint themselves with the guidelines and follow the suggestions that lead to the best results.

Dr. Shear has acted as a paid consultant and speaker for Galderma Canada; and a speaker for Sanofi-Aventis. The University of Toronto Division of Dermatology has received arm's-length support from Galderma, Sanofi-Aventis, and Stiefel, a GSK company.

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2. Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. *J Am Acad Dermatol* 2009;60(5 Suppl):S1–S50.



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Clinical Pearls

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Implement strategies to improve adherence to therapy (e.g., medication reminders, self-monitoring with diaries, support groups, telephone follow-up) to ensure success.
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Treat acne as quickly and as efficiently as possible to achieve the best therapeutic outcomes, and to improve patient satisfaction, limit treatment expenses, and mitigate scarring.