# New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group

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The Global Alliance to Improve Outcomes in Acne published recommendations for the management of acne as a supplement to the *Journal of the American Academy of Dermatology* in 2003. The recommendations incorporated evidence based strategies when possible and the collective clinical experience of the group when evidence was lacking. This update reviews new information about acne pathophysiology and treatment such as lasers and light therapy and relevant topics where published data were sparse in 2003 but are now available including combination therapy, revision of acne scarring, and maintenance therapy. The update also includes a new way of looking at acne as a chronic disease, a discussion of the changing role of antibiotics in acne management as a result of concerns about microbial resistance, and factors that affect adherence to acne treatments. Summary statements and recommendations are provided throughout the update along with an indication of the level of evidence that currently supports each finding. As in the original supplement, the authors have based recommendations on published evidence as much as possible. (J Am Acad Dermatol 2009;60:S1 50.)

***Key words:*** acne; acne scarring; adherence; antibiotic resistance; lasers; maintenance; pathophysiology; retinoids.

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## INTRODUCTION

In 2003, a group of physicians and researchers in the field of acne, known as the Global Alliance to Improve Outcomes in Acne, published recommendations for the management of acne.[1] The goal was to make recommendations that were evidence based when possible and that included input from numerous countries. Since the initial meeting of the Global Alliance in 2001, the group has continued to meet regularly to discuss various aspects of acne management and create educational initiatives for dermatologists around the world. Regional groups in Europe, Asia, and Latin America have been established. Global Alliance members have actively worked with national dermatology societies to formulate guidelines for management of acne that take into account the individual characteristics of the country while harmonizing with the international recommendations. In addition, the Global Alliance presented a written consensus opinion to the US Food and Drug Administration (FDA) Guidance for

*Abbreviations used:*

| | |
|---|---|
| ALA: | aminolevulinic acid |
| AP 1: | activator protein |
| BPO: | benzoyl peroxide |
| $CO_2$: | carbon dioxide |
| ECCA: | échelle d'évaluation Clinique des cicatrices d'acné |
| ECOB: | Elaboration d'un outil d'evaluation de l'observance des traitements medicamenteux |
| Er:YAG: | erbium doped yttrium aluminum garnet |
| FDA: | Food and Drug Administration |
| HLA DR: | Human leukocyte antigen DR |
| ICAM: | intercellular adhesion molecule |
| ICG: | indocyanine green |
| IL: | interleukin |
| IPL: | intense pulsed light |
| MAL: | methyl aminolevulinate |
| MMP: | matrix metalloproteinase |
| PDL: | pulsed dye laser |
| PDT: | photodynamic therapy |
| RF: | radiofrequency |
| TCA: | trichloroacetic acid |
| TLR: | toll like receptor |
| VCAM: | vascular cell adhesion molecule |

investigator for Stiefel and has received honoraria or grant support. Dr Kubba has served as a consultant to Galderma and Schering Plough and in another capacity for Ranbaxy and Janssen Cilag and has received grants and honoraria. Dr Layton has served as an advisor, speaker, and investigator for Galderma and received grants and travel grants and has also been an investigator for Roche, receiving grants. Dr Leyden has served as a consultant and on advisory boards for Allergan, Galderma, Obagi, SkinMedica, Medicis, and Stiefel and received grants and honoraria. Dr Miyachi has served on advisory boards for Galderma, Otsuka, and Sanofi Aventis and has received grants and honoraria. Dr Piquero Martin has served as a speaker for Galderma and received benefits. Dr Ramos e Silva has served on advisory boards for Galderma, Johnson, Stiefel, Novartis, La Roche Posay, and Roche; she has been an investigator for Galderma, Johnson, Stiefel, Novartis, La Roche Posay, Biolab, Aventis, and Pfizer, and has been a speaker for Galderma, Johnson, Stiefel, Novartis, LaRoche Posay, Vichy, and Roche and has received honoraria or grant support. Dr See has received honoraria as a speaker for Galderma and L'Oreal. Dr Shalita has served as a consultant to Galderma, Stiefel, Allergan (including consultancies to companies acquired by these companies), Baxbier, Quinoa, and Ortho and has been an investigator for Galderma, Stiefel, and Allergan and has received grants and honoraria; he has stock options in Medicis. Dr Shear has served on advisory boards for Galderma, and as a consultant and other for Galderma and has received honoraria and residency or fellowship program funding; Dr Shear has also served as a consultant and other for Dermik and received honoraria and residency or fellowship program funding. Dr Thiboutot has been an investigator, consultant, or advisory board member for Allergan, Inc, Arcutis, Inc, Dusa, Inc, Galderma, Inc, Stiefel, Inc, QLT, Inc, and Medicis, Inc and has received honoraria or grant support. Dr Torres Lozada has been a consultant and investigator for Galderma and has received honoraria. Dr Wolf has been an investigator for Galderma and Medicis, an advisory board member, consultant, and speaker for Galderma and Medicis, an advisory board member and consultant for QLT, and a speaker for Stiefel and Dermik; he has received grants and honoraria and has stock in Medicis. Drs Kaminsky and Perez have no conflicts of interest to declare.

Preparation of the manuscript was a joint effort as follows. The manuscript outline, content development and selection of references, review of the data, and generation of the first draft were done in sections, with responsibilities as follows. "Recognizing the chronicity of acne" section: Drs Shear, Finlay, and Gollnick, and Ms Sanders. "Update: Pathogenesis of acne" section: Drs Thiboutot, Kang, and Gollnick, and Ms Sanders. "Update: Treatment of acne" was further subdivided into the following sections. "The changing role of antibiotics in managing acne" section: Drs Layton, Bettoli, Miyachi, Dréno, Perez, and Leyden, and Ms Sanders. "Retinoid based combination therapy for acne" section: Drs Thiboutot, Kaminsky, Gollnick, Miyachi, Wolf, Herane, and Piquero Martin, and Ms Sanders. "Does enough evidence now exist for using lasers and lights to treat inflammatory acne?" section: Drs Leyden, Berson, Kang, See, Shalita, Torres Lozada, and Gollnick, and Ms Sanders. "The role of topical retinoids in acne maintenance therapy" section: Drs Gollnick, Bettoli, Thiboutot, and Leyden, and Ms Sanders. "Management of acne scarring" section: Drs Dréno, Goh, Kubba, Ramos e Silva, and Bettoli, and Ms Sanders. "Optimizing adherence with acne therapy" section: Drs Thiboutot, Dréno, Layton, Herane, and Dr Perez, and Ms Sanders. Ms Valerie Sanders is a medical writing consultant to Galderma International. Changes to the first draft and subsequent drafts were generated by each of the authors. All authors reviewed the complete final draft including all sections.

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Industry on Acne Vulgaris (Docket No. 2005D 0340) regarding development of drugs for acne and design of clinical trials in this arena. A subgroup of European members of the alliance formulated a response to recent changes in the European Union regulations for use of oral isotretinoin. As new issues come up, the alliance will continue to advocate for clinicians who treat patients with acne and the patients' rights to optimal treatment. Finally, the Global Alliance has established a World Wide Web site (www.acneglobalalliance.org), which provides information about the management of acne and recent developments in the field.

The first publication in 2003 encompassed current information about acne pathophysiology and comprehensive treatment recommendations. This edition includes updates on pathophysiology and treatment, including our research into treatments that have recently emerged such as lasers and light therapy and areas where published data were sparse in 2003 but are now available, including combination therapy, revision of acne scarring, and maintenance therapy. In addition to an updated discussion of acne pathophysiology and treatment, we share in this supplement a new way of looking at acne as a chronic disease, a discussion of the changing role of antibiotics in acne management, and factors that affect adherence to acne treatments. As in the original supplement, we have tried to base recommendations on published evidence as much as possible. However, it should be noted that some recommendations are based primarily on our expert opinion (level V evidence) because of a lack of studies and different designs and methodologies of existing studies. We have strived to clearly acknowledge in text which recommendations are based primarily on opinion, citing them as supported by Level V evidence.

In addition, a number of the clinical trials included in our evaluations of data were performed as registration trials for regulatory approval. We acknowledge that a particular type of patient is selected for study and results may not be generalizable to all patients; regulatory bodies typically address this in the package insert. In acne, the registration trial study inclusion and exclusion criteria often exclude patients with cystic acne (>2 nodules or cysts), truncal acne is often not evaluated, and minimum and maximum numbers of inflammatory and noninflammatory lesions at baseline are specified to give an objective measure of acne severity. To our knowledge, there are no data suggesting that acne in various population subgroups adolescent, adult, male, female is different in terms of pathophysiology with the exception of a greater effect of hormones in female patients. Assessment of population differences would be an interesting topic for future studies.

In the case of acne, monotherapy is used relatively rarely despite that regulatory bodies require monotherapy studies for drug approval. Because acne is a multifactorial disease, multiple classes of drugs are typically used in the clinical setting. Indeed, combination therapy is now recommended as the first line approach for acne.[1] In this publication, the Global Alliance group considered the type and severity of acne in making recommendations. The Global Alliance plans to publish additional articles on the topics of hormonal/antiandrogenic therapy and the current use of oral isotretinoin.

The following definitions were used to evaluate the strength of the evidence for recommendations in the supplement:

- I Strong evidence from systematic review of multiple well designed, randomized, controlled trials;
- II Strong evidence from at least one properly designed, randomized, controlled study of appropriate size;
- III Evidence from well designed trials without randomization, single group pre/post, cohort, time series, or matched case controlled studies;
- IV Evidence from well designed nonexperimental studies from more than one center or research group;
- V Opinions of respected authorities, based on clinical evidence, descriptive studies, or reports of expert committees.

## RECOGNIZING THE CHRONICITY OF ACNE

*Editor's note:* This section summarizes ideas that were presented in full in a recent article in the *American Journal of Clinical Dermatology*.[2]

It is important for dermatologists to take the lead in educating other clinicians that acne is often a chronic disease and not just a self limiting disorder of teenagers. For many patients, acne has the following characteristics that have been used to define chronicity[3,4]: a prolonged course, a pattern of recurrence or relapse, manifestation as acute outbreaks or slow onset, and a psychologic and social impact that affects the individual's quality of life. In considering whether acne is a chronic disease, it is interesting to compare it with atopic dermatitis (Table I). The similarities between the conditions are striking and range from underlying pathology (inflammation) to characteristic manifestation (frequently relapsing and recurrent diseases).

**CONSENSUS: Acne Should Be Approached as a Chronic Disease**

*Level of Evidence: V*

➢ Characteristics of acne that define chronic diseases:

- Pattern of recurrence or relapse
- Prolonged course
- Manifestation as acute outbreaks or slow onset
- Psychological and social impact

➢ Acne warrants early and aggressive treatment

➢ Maintenance therapy is often needed for optimal outcomes

Why is this important? Because many of our medical colleagues and a significant proportion of the lay public dismiss acne as a natural part of growing up that has few real consequences. Yet considerable evidence shows that acne can be a psychologically damaging condition that lasts years.[5-11] The members of the Global Alliance believe that acne one of the most common skin diseases treated in routine dermatologic care should be rec ognized and investigated as a chronic disease with psychologic sequelae that do not always correlate with the clinician's assessment of severity at one point in time.[5]

There are no definitive longitudinal studies of the natural history of acne; however, in the group's experience approximately 60% of acne cases are self limiting and can be managed with acute treat ment followed by topical maintenance therapy. In other cases, acne is a disease that requires treatment for a prolonged period. Oral isotretinoin the most effective acne treatment developed to date is ad ministered during a 20 week period and sometimes must be given in repeated courses.[5] Further, as reviewed later in this supplement, recent well con trolled studies have shown that maintenance therapy is an effective strategy to minimize the risk of relapse.[12-14] In addition, the members of the Global Alliance believe that limiting the duration of active acne by effective treatment may, in turn, reduce the likelihood of physical and emotional scarring. For these reasons, we encourage early and aggressive treatment of acne.

How often do negative outcomes occur after acne? That question is difficult to answer definitively. However, there is good evidence that acne can persist into adult years in as many as 50% of individuals.[7,15-18] Negative psychologic outcomes, including anxiety, depression, and social withdrawal, have all been reported among individuals with acne and acne scars.[7,9,10] Physical scars, persistent hyperpigmentation, or both are not uncommon sequelae of acne and are usually expensive and difficult to treat effectively. The effects of acne can persist for many years, even among individuals who had self limited adolescent acne.

**Table I.** Comparison of chronicity in acne and atopic dermatitis

| | Acne | Atopic dermatitis |
|---|---|---|
| Basic character | Inflammatory | Inflammatory |
| Duration | >3 mos → 5-30 years | >3 mo → 5-40 years |
| Genetic influence | Yes, particularly in long-term courses; thought to be polygenic | Yes, thought to be polygenic |
| Age at onset, y | ~10 | ~1 |
| Self-limiting? | In ~80% of cases by third decade of life | In ~80% of cases by second decade of life |
| Counseling? | Intervals/years | Intervals/years |
| Medication | Continuously/ intervals | Continuously/ intervals |
| Social impact | Yes | Yes |
| Psychologic impact | Yes | Yes |
| Postdisease sequelae | Yes | |
| Physical scarring | Yes | Yes |
| Psychologic | | Yes |

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Unfortunately, the reason why acne becomes chronic in some patients is not well understood and it is currently difficult to determine which patients will have a chronic course of the disease. Factors that have been linked to a chronic course include stress related production of adrenal andro gens,[19] *Propionibacterium acnes* colonization,[20] fa milial background,[7] and specific subtypes of acne (conglobata, keloidal, inversa, androgenic, scalp folliculitis, and chloracne).[21,22] The members of the Global Alliance advocate further study to determine the link between these and other characteristics and the development of chronic acne.

In summary, dermatologists are aware that acne is a chronic disease with important ramifications. We are charged in our role as skin experts with the mission of helping other health care professionals and patients to achieve a better understanding of acne and improve awareness of the highly effective treatments that are available. We must also be vigilant in ensuring that insurers and government regulatory bodies are aware of the impact and import of acne. Because the physical and emotional

sequelae associated with acne can last for many years, insurers need to be encouraged to provide reimbursement for acute and maintenance acne treatments that have been proven effective in clinical trials.

## UPDATE: PATHOGENESIS OF ACNE

More detailed information regarding the molecular events contributing to the pathogenesis of acne has emerged since 2003. There are 4 primary pathogenic factors, which interact in complex manner to produce acne lesions: (1) sebum production by the sebaceous gland; (2) *P acnes* follicular colonization; (3) alteration in the keratinization process; and (4) release of inflammatory mediators into the skin. Now, cellular culture studies have provided more information about the role of sebaceous lipids and inflammatory mediators including MMPs.

Jeremy et al[23] investigated the initiating events for acne lesions, and found that immune changes and inflammatory responses occur before hyperproliferation of keratinocytes, with a pattern similar to a type IV delayed hypersensitivity response. The immune response is led by $CD4^+$ lymphocytes and macrophages.[23] These researchers hypothesize that the subsequent production of cytokines activates local endothelial cells, up regulating inflammatory vascular markers (E selectin, vascular cell adhesion molecule 1 [VCAM 1], intercellular adhesion molecule 1 [ICAM 1], and human leukocyte antigen DR [HLA DR]) in the vasculature around the pilosebaceous follicle.[23] They further have postulated that the entire process is initiated by interleukin (IL) 1$\alpha$ up regulation in response to a relative linoleic acid deficiency caused by excess sebum and perturbation of barrier function within the follicle.[23]

More than a decade ago, an in vitro study by Vowels et al[24] demonstrated the presence of a soluble factor of *P acnes* that induced proinflammatory cytokine production in human monocytic cell lines. Although distinct from lipopolysaccharide, this soluble factor had similar characteristics, in that its activity was dependent on the presence of CD14, a so called pattern recognition receptor for lipopolysaccharide and other lipid containing ligands. This *P acnes* product induced the synthesis of tumor necrosis factor $\alpha$ and IL 1$\beta$ in the cell lines. Later research showed that the cytokine induction by *P acnes* was occurring through TLR 2.[25] TLR, a mammalian homologue of a drosophila protein known as toll, has emerged as a key regulator of host responses to infection.[26] This transmembrane protein has a cytoplasmic portion that is homologous to the IL 1 receptor and thus could trigger a signaling cascade that activates nuclear factor $\kappa$B. A recent in vivo study by Jugeau et al[27] demonstrated that these events occur in inflammatory lesions of patients with facial acne and confirmed the earlier observations of Kim et al[25] in acne lesions. This provided additional evidence that inflammatory cytokines, working via autocrine and paracrine mechanisms through their respective receptors, amplify the signaling pathways that activate the activator protein (AP) 1 transcription factor.[28] Activation of AP 1 induces MMP genes, whose products degrade and alter the dermal matrix.[28] Retinoids are known to inhibit AP 1.[29] Very recent studies indicate that retinoids can induce monocytes to develop into $CD209^+$ macrophages that phagocytose *P acnes* bacteria.[30] These data further substantiate how such currently available treatments as topical retinoids can have anti inflammatory activity against acne. In addition, they may help to explain why acne can flare after initiation of therapy; for example, disruption of sebocytes may result in release of proinflammatory molecules, leading to the clinical result of increased inflammation in some patients.

More has been learned about the role of seborrhea in acne as well. Sebaceous lipids are at least partly regulated by peroxisome proliferator activated receptors and sterol response element binding proteins.[31,32] Peroxisome proliferator activated receptor nuclear receptors act in concert with retinoid X receptors to regulate epidermal growth and differentiation and lipid metabolism.[31] Sterol response element binding proteins mediate the increase in sebaceous lipid formation induced by insulin like growth factor 1.[32]

In parallel, research into the functions of the sebaceous gland has yielded exciting information about the central role these glands play in regulation of skin functions.[33] The sebaceous gland regulates independent endocrine functions of the skin and has a significant role in hormonally induced aging of skin.[34,35] In addition, the sebaceous gland has both direct and indirect antibacterial activities. Sapienic acid, a lipid in sebum, has innate antimicrobial activity and is up regulated by activation of TLR 2 by skin bacteria.[36,37] Further, the sebaceous gland has ubiquitous expression of antibacterial peptides and proinflammatory cytokines/chemokines; these substances are induced in sebocytes by the presence of bacteria.[38] The sebaceous gland acts as an independent endocrine organ in response to changes in androgens and hormones, and is the control center for a complex regulatory neuropeptide program that acts like the hypothalamus pituitary adrenal axis.[33] This aspect of sebaceous gland function is primarily influenced by corticotrophin releasing hormone, its binding protein, and

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