An update on the pathogenesis and management of acne vulgaris

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Acne vulgaris is an easily recognizable dermatologic disease. It is also very common. Acne is seen in nearly 100% of individuals at some time during their lives. Small, noninflamed acne lesions may not be more than a slight nuisance but, in individuals with more severe inflammatory nodular acne, pain, social embarrassment, and both physical and psychological scarring can be life altering. Fortunately, our understanding of the pathogenesis of acne has progressed and our therapeutic armamentarium has greatly expanded in the last twenty-five years.

The four key pathogenetic factors of acne have been recognized for decades. These include follicular epithelial hyperproliferation and resultant follicular plugging, excess sebum, inflammation, and the presence and activity of *Propionibacterium acnes* (Table I). The earliest microscopic lesion observed in acne vulgaris is the microcomedo. This lesion is characterized by follicular plugging. Inflammation and the bacteria, *P acnes*, are not observed. The stimulus for microcomedo formation is still unknown. Leading hypotheses implicate androgen hormones, alterations in follicular linoleic acid levels, and the inflammatory cytokine interleukin-1α (IL-1α). The microcomedo is the precursor of other acne lesions. With time, the microcomedo fills with *P acnes*, whose cell wall and biological byproducts are chemoattractant and proinflammatory. As a result, inflammatory cells surround the follicle, diffuse through the follicular wall, and produce enzymes that disrupt the follicular wall. The degree of inflammation seen in acne vulgaris may be dependent upon individual immune responsiveness to *P acnes*. Likewise, there may be individual variability in the response of the sebaceous gland androgen receptor to circulating androgens.

Recently, the toll-like receptor 2 (TLR-2) has been implicated in the pathogenesis of acne. TLR-2 is a pattern recognition receptor that is activated by *P acnes*. When bound, TLR-2 activates a transcription factor that upregulates production and the release of proinflammatory cytokines like interleukin-12 and interleukin-8 from monocytes. TLR-2 is expressed on infiltrating inflammatory cells around the pilosebaceous follicle in those with acne. Its expression increases as the acne lesion ages and becomes more inflamed.[1]

The role of androgen hormones in the pathogenesis of acne has also been carefully evaluated. Overall, circulating androgen hormone levels are normal in individuals with acne who do not have other signs or symptoms of hyperandrogenism. The enzyme 5α-reductase type 1 has been studied in those with and without acne. 5α-reductase type 1 is present in the sebaceous gland and converts testosterone to the more potent androgen receptor ligand, dihydrotestosterone (DHT). It has been hypothesized that those with acne might have more active 5α-reductase type 1. However, no statistically significant difference in enzyme activity has been observed to date between those with and without acne, but subject numbers have been very low.[2]

The past twenty-five years have brought about significant changes in the treatment of acne. No other group of medications has altered the management of acne more than the retinoids. The topical retinoids became mainstream acne treatment in the early 1980s, but problems with skin irritation limited their utility in some individuals. Adapalene, a topical retinoid by function, was introduced in the mid-1990s, followed quickly by formulations of tretinoin touted to be less irritating. Tazarotene was soon added to the list of topical retinoids effective in the treatment of acne. Topical retinoids have been well accepted as the treatment of choice for comedonal acne since their inception. Recently, they have been promoted as an effective treatment for inflammatory acne, alone or in combination with other acne

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Table I. Acne treatments and their mechanism of action in acne vulgaris

Benzoyl peroxide	Antimicrobial
	Weakly comedolytic
Topical retinoids	Comedolytic
	Anti-inflammatory
Systemic antibiotics	Anti-inflammatory
	Antimicrobial
Oral contraceptives	Sebosuppressive
Systemic retinoids	Comedolytic
	Anti-inflammatory
	Sebosuppressive
	Indirectly antimicrobial

Acne vulgaris is a multifactorial disease process. Multiple treatments are available that target one or a few of the key pathogenetic elements. The most effective available drug, the systemic retinoid isotretinoin, targets all four of the primary follicular changes observed in acne vulgaris.

medications, and have been recommended for maintenance therapy after acne has been effectively controlled.

Isotretinoin, a systemic retinoid, was approved for use in acne vulgaris in 1982. It is arguably the most effective acne medication available, offering a durable clearing of acne lesions in 85% of its users. A long list of potential side effects limits its use to those individuals with severe, scarring acne or to individuals who do not respond to first-line topical and systemic acne treatments. Of the potential side effects, teratogenic effects and potential psychiatric disturbances have received the most attention in the lay press. The alleged risk of depression and other psychiatric disturbances and a need to decrease the number of isotretinoin-exposed pregnancies has prompted the development of a national registry of prescribing physicians.

Antibiotics continue to play an integral role in the management of acne. Tetracycline has fallen from favor in the face of increasing *P acnes* antibiotic resistance. Doxycycline and minocycline have replaced tetracycline as first-line anti-acne antibiotics. Low-dose doxycycline (doses below the minimal inhibitory concentration for *P acnes*) have recently been shown to be effective in the treatment of acne. These doses of doxycycline do not alter the microbial colony counts in acne patients and yet acne improves. Low-dose antibiotics maintain their anti-inflammatory properties and, though they do not decrease microbial colony counts, likely render *P acnes* less biologically active and less capable of inciting further inflammation.[3]

Long-term use of antibiotics in the acne population has raised concerns regarding the development of colonization with potential pathogens and bacterial resistance. *P acnes* resistance to tetracycline is well known to dermatologists. However, it is the antibiotic resistance of potential pathogens like *Streptococcus pyogenes* and *Staphylococcus aureus* that cause concern. A recent report found a threefold increase in the prevalence of *Streptococcus pyogenes* in the oropharynx of those acne patients treated with systemic or topical antibiotics compared with acne patients not receiving antibiotics. Eighty-five percent of *S pyogenes* cultured from those individuals on antibiotics was resistant to at least one tetracycline antibiotic. Although no significant difference in the frequency of illness was observed when the two groups were surveyed, it cannot be assumed that the changes in microflora and bacterial resistance in those on antibiotics for acne is not clinically significant.[4]

Topical benzoyl peroxides have been used to treat acne for years. Benzoyl peroxides are known to be antimicrobial and also have weak comedolytic properties. Despite the development of better comedolytic agents and the presence of numerous antibiotics and antimicrobials marketed for acne, benzoyl peroxides may be an even more important acne treatment option now than before. While *P acnes* has developed a considerable amount of resistance to erythromycin and tetracycline, benzoyl peroxide continues to effectively eradicate this acne-associated bacteria. Bacterial resistance to benzoyl peroxide has not been reported. In fact, combining benzoyl peroxide with topical or systemic antibiotics may decrease the development of resistance to the co-administered antibiotic.

Oral contraceptives have become an accepted therapeutic alternative for the treatment of acne in women. All combination oral contraceptive pills have a net effect of increasing sex hormone binding globulin and decreasing circulating free testosterone and therefore, have the potential to improve acne. A unique combination oral contraceptive, Yasmin, combines ethinyl estradiol with the progestin drospirenone. Drospirenone is an analog of spironolactone and has antiandrogenic and antimineralocorticoid properties. The drospirenone component in Yasmin is equivalent to 25 mg of spironolactone. Yasmin has been compared to a cyproterone acetate-containing oral contraceptive in the treatment of acne vulgaris and was found to be at least equally effective.[5]

Procedure-oriented acne treatments are being introduced nearly everyday. Light, laser, and photodynamic treatments are all currently being utilized in the treatment of acne. Blue and red light target different pathogenetic factors in acne. Blue light (405-420nm) reacts with porphyrins produced by

P acnes, creating reactive oxygen species that damage the bacterial cell wall and cause bacterial death. Red light (660nm) is anti-inflammatory. Both wavelengths of light may improve acne in some individuals. Clinical trials are few in number and offer no long-term follow-up to date. Photodynamic therapy (PDT) again utilizes blue light reacting with a porphyrin in the sebaceous gland. Sebaceous gland damage and destruction is the hypothesized mechanism of action of PDT in acne vulgaris. Controlled clinical trials are lacking at this time. Nonablative radiofrequency for the treatment of moderate to severe acne was recently reported in the dermatology literature. Nonablative radiofrequency produces dermal heat without causing epidermal damage. It is hypothesized to target the sebaceous gland in acne and to remodel acne scarring. Twenty-two subjects with moderate to severe, scarring, cystic, active acne were enrolled in the study. Study subjects received one initial treatment that lasted 30 to 45 minutes. Pain was managed with topical ELA-max. Patients were offered a second treatment after one month if no improvement was observed. Thirteen patients had only one treatment while only two patients required three treatment sessions. Seventy-five percent reduction in active acne lesion counts was measured in 18 of 22 subjects. Some improvement in acne scarring was also observed. Long-term results were not reported.[6] Lasers are also being used to cause sebaceous gland damage and destruction in individuals with acne vulgaris. Controlled clinical studies are still needed.

Remarkable progress has been made in our understanding of the pathogenesis of acne over the last twenty-five years, and improved treatment alternatives have changed the practice of dermatology and the lives of many of our patients. Much remains unknown. The search for the initial stimulus of microcomedo formation will continue. What is the role of IL-1α? What is the role of androgen hormones? What factors regulate the sebaceous gland?

Effective treatments that offer durable responses and have minimal side effects are still needed. The exact mechanism of action of isotretinoin is still unknown. It is unclear why treatment results are maintained in many individuals after discontinuation of the drug. A greater understanding of the mechanism of action of isotretinoin in acne will help us to design new drugs and procedures that are as effective as isotretinoin but avoid the unwanted side effects and associated risks.

Procedure-oriented acne treatments are not required to meet the stringent criteria set forth for prescription medications to become approved by the Food and Drug Administration. In order for these procedures to meaningfully contribute to the body of knowledge of acne and to help those individuals who suffer from acne, scientifically controlled clinical trials must be performed.

Much has been learned in the recent past about acne but even more is still unknown. Perhaps the next twenty-five years holds the key that will unlock many of the remaining mysteries. Perhaps we will find that key tomorrow.

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