Acne Vulgaris: Pathogenesis, Treatment, and Needs Assessment

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- Epidemiology
- Treatment

Acne vulgaris is a common skin condition with substantial cutaneous and psychologic disease burden. Studies suggest that the emotional impact of acne is comparable to that experienced by patients with systemic diseases, like diabetes and epilepsy.\textsuperscript{1–3} In conjunction with the considerable personal burden experienced by patients with acne, acne vulgaris also accounts for substantial societal and health care burden. Americans use more than 5 million physician visits for acne each year, leading to annual direct costs in excess of $2 billion.\textsuperscript{4,5} Acne is the most common diagnosis made by dermatologists and is also commonly made by nondermatologist physicians.\textsuperscript{6,7} The pathogenesis and existing treatment strategies for acne are complex.\textsuperscript{8} This article discusses the epidemiology, pathogenesis, and treatment of acne vulgaris. The burden of disease in the United States and future directions in the management of acne is also addressed.

EPIDEMIOLOGY

Acne is a highly common skin condition. Still, estimates of acne prevalence vary substantially given the absence of a universally accepted diagnostic or grading schema. Additionally, estimates continue to change as the prevalence of acne decreases secondary to improved treatment modalities.\textsuperscript{9} Acne is most common in adolescents, affecting approximately 85% of teenagers.\textsuperscript{9,10} Acne prevalence after adolescence decreases with increasing age, but disease burden in younger adults is still quite high.\textsuperscript{3} A common misconception by the medical and lay community is that acne is a self-limited teenage disease and, thus, does not warrant attention as a chronic disease. Nevertheless, the chronicity of many cases of acne as well as the well-documented psychologic effects of chronic acne contributes to the burden of the disease.\textsuperscript{2,3,11}

The average age of onset of acne is 11 years in girls and 12 years in boys.\textsuperscript{12,13} Acne is increasing in children of younger ages, with the appearance of acne in patients as young as 8 or 9 years of age. This trend toward earlier development of acne is thought to be related to the decreasing age-of-onset of puberty that has been observed in the United States.\textsuperscript{14} Acne is more common in males in adolescence and early adulthood, which
is a trend that reverses with increasing age.\textsuperscript{12,13} It is well known that adult acne is more common in women. Adult acne typically represents chronic acne persisting from adolescence, not new-onset disease.\textsuperscript{15,16}

Other factors impacting acne prevalence and severity include ethnicity and genetic propensity. Acne age of onset and disease character vary among patients of different ethnicities. Scarring and pigmentary changes are common in skin of color. Propensity to scar and to develop hyperpigmentation is highest among Hispanic and African American patients, respectively.\textsuperscript{12,17} These long-term disease consequences are challenging to treat and contribute to the disease burden. In addition, genetic factors impact the propensity to develop acne. Adolescent and adult acne is more common in children of parents with a history of acne.\textsuperscript{12,18,19}

Several modifiable factors alter acne risk. Cigarette smoking, for example, raises acne risk with disease severity worsening in a dose-dependent fashion with increasing number of cigarettes smoked daily.\textsuperscript{13} Although evidence regarding the impact of dietary factors on acne is equivocal, studies suggest that dairy intake increases acne risk.\textsuperscript{20–22} Finally, traditional opinion in dermatology holds that acne tends to improve during summer months when sun exposure is greater.\textsuperscript{23} This finding is supported by an observed seasonal decrease in physician visits for acne during summer months.\textsuperscript{24} Nevertheless, no studies exist to support this association and use of UV light to treat acne has been rejected.\textsuperscript{23} Undoubtedly, acne is a complex disease process influenced by both genetic and environmental factors.

**PATHOGENESIS**

The pathogenesis of acne is a result of multifaceted processes within the pilosebaceous unit resulting in bacterial overgrowth and inflammation. This condition typically develops at the time of the pubertal transition when changes in the body’s hormonal milieu alter pilosebaceous gland function. Initially, follicular epithelial cells differentiate abnormally and form tighter intracellular adhesions and, therefore, are shed less readily. This process leads to the development of hyperkeratotic plugs, or microcomedones, which enlarge progressively to form noninflammatory, closed or open comedones.\textsuperscript{25} Circulating and cutaneously derived androgens, often named the primary inciting factor in the development of acne, induce sebum production, further contributing to the development of comedones.\textsuperscript{26} Conditions, such as polycystic ovarian syndrome, congenital adrenal hyperplasia, and various endocrine tumors, result in a higher circulating level of androgens and are associated with the development of acne vulgaris.\textsuperscript{27}

The corporal distribution of acne depends on pilosebaceous gland density and morphology and, thus, is common in regions where these structures are largest and most abundant: the face, chest, neck, and back. Noninflammatory acne is characterized by the formation of open or closed comedones. Open comedones, or blackheads, demonstrate darkly colored hyperkeratotic plugs within the follicular opening. This dark coloration is related to the oxidation of melanin and not dirt, as is a common public misconception. Closed comedones, or whiteheads, are white to flesh toned in color and seem not to have a central open pore.\textsuperscript{25}

Changes in the skin’s natural flora accompany this androgen-related increase in sebum production. Propionibacterium acnes, a normal component of the cutaneous flora, inhabits the pilosebaceous unit using lipid-rich sebum as a nutrient source. \textit{P. acnes}, therefore, flourishes in the presence of increased sebum production, leading to inflammation via complement activation and the release of metabolic byproducts, proteases, and neutrophil-attracting chemotactic factors.\textsuperscript{25,28} Inflammatory acne vulgaris lesions, such as papules, pustules, nodules, or cysts, develop when comedones rupture and contents of the pilosebaceous unit spill into the surrounding dermis.\textsuperscript{25,29} In severe cases, adjacent cysts may coalesce to form channels or draining sinuses. Inflammatory acne may produce cutaneous scarring or hyperpigmentation that persists long after acne resolution.\textsuperscript{25}

**PREVENTION**

External factors play an important role in the development of acne lesions. Cigarette smoking and dietary factors increase acne risk and disease severity. In addition, certain skin and hair products and use of occlusive clothing articles contribute to acne development. The removal of any of these factors may lead to an improvement in disease severity.

The link between smoking and acne is well established.\textsuperscript{13} Even though smoking avoidance and cessation should be encouraged in all patients, this preventive message is especially important for patients suffering from acne. Practitioners should emphasize not only that smoking increases acne risk but also that a dose-dependent relationship exists between daily cigarette use and acne disease severity.
The controversial relationship between diet and acne has been studied for many years. There is no reputable evidence to support a link between acne and chocolate. Recently, however, studies have suggested an association between milk and acne.20–22 This finding is based on increased levels of insulin-like growth factor 1 in milk causing an increase in circulating androgens. Associations of omega-3 fatty acids, antioxidants, zinc, vitamin A, and iodine with acne have also been proposed. However, all of these areas require further research.30 Dietary modification alone is not adequate for acne prevention regardless of the association between diet and acne. Individuals with acne wishing to make dietary changes should focus on the avoidance of dairy products as perhaps the most evidence-based intervention.

Facial and hair products, especially cosmetics and hair products containing oils, may lead to an exacerbation of acne lesions.17,31 In addition, repeated scrubbing with soaps, detergents, and other agents can cause trauma to underlying comedones, thereby increasing inflammation. Thus, individuals with acne should select oil-free or noncomedogenic products and refrain from aggressively rubbing the face.32 Other factors also contribute to pore occlusion, including tight clothing and head gear. Hence, these articles should be avoided when possible.

TREATMENT

In the United States, there is an overabundance of treatment recommendations for patients with acne. Unfortunately, few of these recommendations are evidenced based and comparative studies are limited.33 In fact, in 2009, the Institute of Medicine listed acne as a priority for comparative effectiveness research evaluating treatment regimens.34 Recently published treatment algorithms include A Global Alliance to Improve Outcomes in Acne, those endorsed by the American Academy of Dermatology, and recommendations from a European expert group on oral antibiotics to treat acne.32,35,36 These recommendations are based on expert opinion given the limited evidence available. All of the guidelines recommend similar approaches focusing on acne severity and degree of inflammation. In addition, acne treatment recommendations may be based on skin type, clinical classification of acne, and preexisting acne scarring.37 Treatment options include proper skin care, topical and oral antimicrobials, topical and systemic retinoids, benzoyl peroxide, and oral contraceptives for female patients. These treatments are often used in combination to achieve disease resolution.

A primary initial treatment approach is proper skin care. This care includes eliminating the aforementioned extrinsic factors as well as encouraging proper skin hygiene and adherence to prescribed acne treatment regimens. Although it was previously thought that excessive skin cleansing contributes to the formation of acne, several small studies indicate that facial cleansing, even when performed up to 4 times daily, is not harmful and may, in fact, diminish acne severity.38–40 Patient education in proper hygiene includes counseling regarding appropriate skin cleanser and moisturizer selection.41

If skin care alone does not lead to the resolution of cutaneous lesions, topical and systemic antimicrobials may be used. Topical antibiotics may be used to treat mild to moderate acne. Systemic antibiotics are indicated when acne is moderate to severe or if disease manifestations are producing marked psychosocial stress for patients.28 The purpose of this treatment modality is to decrease the presence of *P. acnes* on the skin surface and within the pilosebaceous unit.42 Antibiotics confer more than antimicrobial properties. They also produce antiinflammatory effects, inhibit neutrophil chemotaxis, and alter compliment pathways, all of which aid in the treatment of acne.28 Various classes of antibiotics, such as sulfonamides, macrolides, tetracyclines, and dapsone, may be used to treat acne.28,42

Widespread and long-term use of antibiotics has led to the development of *P. acnes* resistance and has also been associated with *Staphylococcus* resistance.28,43,44 Thus, when treating with antimicrobials, the prescribing clinician must consider not only local patterns of resistance but also patient adherence to a regimen that will not promote selection for resistant bacterial strains. It is also important to avoid protracted antibiotic courses. Monotherapy with antimicrobials should be avoided, especially when using macrolides that are most often associated with the development of resistance.28,44 Instead, successful treatment is often seen when pairing antimicrobials with benzoyl peroxide, hormonal therapies, and retinoid preparations.28,42

In women with mild to moderate acne, combined oral contraceptives (COCs) can be used. A recent Cochrane review concluded that this method of treatment reduces acne severity when compared with placebo.45 Even though androgen levels are often normal in women with acne vulgaris, hormonal therapies combating androgens seem to benefit these patients.46 Progestins tend to be proandrogenic but most COCs are estrogen dominant. Estrogen containing oral contraceptives increase circulating levels of
steroid hormone binding globulin which results in lower circulating levels of testosterone. Different COCs contain varying levels of progestins and the implications of this require further research. In women with mild to moderate acne who do not desire childbearing, COCs are a good treatment recommendation. Oral contraceptives are often paired with other acne therapies.

Topical retinoids represent the most commonly prescribed treatment option because they are effective in both the treatment and prevention of acne. The mechanism of action of retinoids involves preventing the primary acne lesion, which decreases inflammation. This drug class is an excellent choice for both initial and maintenance therapy and assists many patients in achieving adequate disease control. Depending on the case, topical retinoids can be paired with benzoyl peroxide, antimicrobials, or with oral contraceptives.

Finally, oral isotretinoin is an option for severe, refractory acne. The mechanism of action includes decreasing sebaceous gland activity with a resultant decrease in sebum secretion. This action effectively diminishes overgrowth of P. acnes, which is a key pathogenic factor. The drug also inhibits keratinocyte hyperplasia and instead promotes normal differentiation. Isotretinoin must be prescribed carefully because it carries several black box warnings, including teratogenicity, possible change in mood status, and hypertriglyceridemia, among others. This drug is the only acne treatment option that permanently changes the course of the disorder. However, because of the considerable side effects, it should only be used in those with refractory nodular acne.

Given the increasing trend toward treatment with several agents simultaneously, providers have come to rely on the use of combination agents in the treatment of acne. These agents include pairings of topical antibiotics with benzoyl peroxide, topical antibiotics with retinoids, and others. Use of combined agents has been demonstrated to improve patient adherence to prescribed regimens. Given that poor adherence to complex medication regimens limits treatment efficacy and contributes to the chronicity and burden of acne, providers should aim to simplify treatment regimens and use combined agents when feasible.

ACNE SCARRING

Despite the many treatment options, acne scars still develop in some patients. They result from skin damage during the healing process of acne. Acne scars are divided into 2 groups: more common atrophic scars and hypertrophic scars. Treatments for acne scarring include, but are not limited to, topical treatments, chemical peels, dermabrasion, laser, and dermal grafting. Unfortunately, there are no well-accepted guidelines to optimize acne scar treatment. Additional research is required to determine cost-effectiveness and establish the duration of treatment effects.

BURDEN OF TREATMENT

The annual cost of acne treatment is quite high given the prevalence and chronicity of the disease. Acne represents the most common dermatologic diagnosis in the United States. A study based on data from 2004 estimates that the annual direct cost of acne management is more than $2.5 billion. Acne ranks second only to skin ulcers and wounds in annual cost burden for dermatologic illness.

In addition to the high cost burden, the treatment of acne produces heavy physician demands. Acne accounts for more than 5 million physician visits annually, or approximately 8% of all dermatologic health care visits. Two-thirds of physician visits for acne are made by women, suggesting that women are more likely than men to seek medical care for acne. Contrary to the perception of acne as a disease of adolescents only, individuals aged older than 18 years account for more than 60% of acne-related visits. Nevertheless, the health care burden of adolescent acne is substantial, with patients aged 12 to 17 years composing nearly 40% of the visits. Although recent studies have demonstrated an increase in acne prevalence for children aged younger than 12 years, these patients account for the minority of health care visits or less than 2% of all physician visits for acne.

AVAILABLE SERVICES

Acne vulgaris is managed in the outpatient setting by both specialist and generalist physicians. Dermatologists provide approximately two-thirds of all acne care in the United States, followed by pediatricians (16%), general/family practitioners (12%), internists (5%), and obstetricians/gynecologists (1%). Long wait times and poor geographic distribution of the dermatologic workforce are 2 factors thought to promote the use of nondermatologist care in acne treatment. Furthermore, several characteristics, including being younger than 18 years of age, Hispanic ethnicity, receipt of care in the West or Midwest, and the use of public medical insurance, are predictive of nondermatologist acne care.
Use of nondermatologist care in acne treatment is relevant because it may not be equivalent to the care provided by dermatologists. Studies report differences in prescribing patterns and varying regimen complexity between dermatologists and general practitioners. In particular, generalists are less likely to prescribe topical retinoids and are more likely to prescribe antibiotic monotherapy, which are trends not in line with the present recommendations.47,58

Overall, generalists receive limited training in the treatment of dermatologic disease. US medical schools provide on average only 21 hours of dermatology training before graduation, and dermatologic training in pediatric and internal medicine residencies is limited.59–61 Dermatologists diagnose acne many times more frequently than their generalist counterparts and this quantity of experience also contributes to the expertise of dermatologists in treating acne.7,62 Even so, the role of nondermatologist care of acne should not be undervalued, given the substantial burden of acne. Medical school and residency training programs should place greater emphasis on dermatologic education. Future efforts to develop standardized, evidence-based acne treatment guidelines may assist nondermatologists in providing comparable acne care.

In addition to the acne treatment by physicians, there has also been a growing trend toward the use of physician assistants (PAs) and other midlevel providers in the management of dermatologic disease. In fact, dermatologists are second only to ophthalmologists in their use of PAs. In 1997, 1 in every 32 patients visiting a dermatology clinic was seen by a PA, which is a proportion that is thought to have increased markedly since that time. PAs work under the supervision of a physician; however, more than one-quarter of patients seeing a PA for dermatologic complaints are not directly evaluated by a physician.63 To the authors’ knowledge, no exact figures are available for the use of PAs in the treatment of acne specifically. Nevertheless, anecdotal experience indicates that acne is a condition commonly managed by dermatology PAs and that the use of PAs to evaluate acne may diminish the costs associated with acne management. Further analyses of the efficacy and cost of PA management of acne are warranted.

In addition to the care resources offered through physicians and midlevel providers, many online resources are available to patients suffering from acne. The American Academy of Dermatology (www.aad.org) offers detailed patient information on acne and also hosts a searchable database that aids patients in locating dermatologists in their geographic region. Acne-Net (http://skincarephysicians.com/acnenet/index.html) provides similar patient material online. Social networking and other online media sources host abundant content describing acne management. Although much of this online content is unregulated and should be interpreted carefully, numerous reliable health information sources exist. Physicians should be aware of the many accurate online resources to which they can direct patients as well as the unregulated content their patients may be accessing.

FUTURE DIRECTIONS

Going forward, several priorities should guide acne research and management efforts. First, it is imperative that comparative effectiveness research is emphasized and evidence-based treatment strategies are established for acne. Not only will this enhance patient outcomes but this will also allow for better control of the costs and physician demands associated with acne treatment. The establishment of optimal treatment regimens would be expected to diminish the chronicity and, hence, burden of acne disease. Furthermore, standardized recommendations would help enable nondermatologist physicians to provide appropriate care and assist in meeting the demands of acne management. Likewise, medical school and residency training programs must emphasize dermatology education. Generalists commonly manage dermatologic illness and their ability to effectively do so relies heavily on adequate training.

Efforts to explore alternative care resources should be supported. Already, the use of PAs and other midlevel providers has been established in dermatologic practice. Further analyses of the efficacy and cost-effectiveness of midlevel provider care should be pursued. Additionally, in recent years, the use of the teledermatology and Internet-based dermatologic care in the treatment of acne has been explored. The use of digital images to monitor treatment progress has been proposed and may be reliable with certain assessment measures, such as total inflammatory lesion count.64 Similarly, online follow-up visits for acne have been demonstrated to produce equivalent patient outcomes.65 The use of digital and online resources to treat acne may diminish cost burden and assist in making dermatology services available to patients in regions with limited dermatologic resources.

Finally, cellular phone and Internet technology may be used to promote adherence to treatment regimens through the use of patient reminders.
Adolescents and young adults, the patients most impacted by acne, are simultaneously highly receptive to the use of technology and prone to medication noncompliance. Improved treatment adherence could help to diminish the acne burden of disease. Physicians must proceed creatively yet cautiously as they develop new approaches to manage acne and control disease burden.

SUMMARY
Acne vulgaris is a common dermatologic disease that results in high monetary and physician use demands in the United States. The pathogenesis and treatment of acne is complex and requires ongoing research to establish best-practice guidelines. In the meantime, physicians should emphasize existing evidence-based recommendations, including the use of topical retinoids and avoidance of antibiotic monotherapy, in the treatment of acne. Moreover, clinicians must continue to pursue innovative strategies, such as the use of nonphysician providers, teledermatology, and other technologic resources, as a means by which to enhance acne management and limit the substantial burden of this prevalent disease.

REFERENCES
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