Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (10) Issue (1) (2025), (47- 52) **online: ISSN 2356–976x**

http://bjas.bu.edu.eg
Medical and Health Science

Acne Vulgaris: Pathogenesis, Clinical Manifestations and Therapeutic Lines

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Abstract:
One example of a chronic inflammatory condition is acne vulgaris. Causes of chronic acne include overproduction of sebum, abnormal follicular infundibulum keratinisation, the spread of bacteria, and subsequent inflammation, as well as endocrinological variables like androgens. The pathophysiology of this condition usually starts in the early teen years but may continue far into adulthood. The most common areas to find lesions are on the chest, upper back, neck, and face. Among the many types of acne, you may find those specific to certain situations or occupations, such as neonatal or infantile acne, acne conglobata, acne fulminans, acne mechanica, excoriated acne, chloracne, or acne produced by certain medications, such as anabolic steroids, corticosteroids, lithium, or phenytoin. To lessen the emotional and social toll of the condition, there are a number of helpful medication options, both topically and systemically applied. Oral medications (such as tetracyclines, macrolides, and isotretinoin) and hormonal treatments (such as oral contraceptives and systemic glucocorticoids or GnRH agonists) are the most common methods of treating acne vulgaris, although topical medications (like benzoyl peroxide (BP), topical antibiotics, retinoids, azelaic acid, dapsone, etc.) and oral medications in general are also used frequently.
The purpose of this review article is to identify the causes, symptoms, and treatment options for acne vulgaris.

Keywords: Acne vulgaris, Pathogenesis, Clinical manifestations, Therapeutic lines, Inflammation

Introduction

The pilosebaceous follicles are the targets of the chronic inflammatory skin disorder known as acne vulgaris, which affects individuals globally. Predicted to impact 9.4% of the world's population, acne is the eighth most common skin illness. Acne affects over 85% of teens and may even last into adulthood; it's more common in girls and women, and it's the reason why dermatologists see so many patients with this condition. Inflammatory lesions, such as papules, pustules, nodules, and cysts, cause scarring and pigmentation of the skin and need long-term, ongoing treatment, whereas non-inflammatory lesions, including open/black and closed/white comedones, do not. The most common areas to find lesions are on the chest, upper back, neck, and face. Among the many types of acne, you may find those specific to certain situations or occupations, such as neonatal or infantile acne, acne conglobata, acne fulminans, acne mechanica, excoriated acne, chloracne, or acne produced by certain medications, such as anabolic steroids, corticosteroids, lithium, or phenytoin. Clinical presentation, severity, and associated symptoms may differentiate these variants from acne vulgaris, which they resemble histologically and clinically. Although there is currently no known way to prevent or cure acne, there are effective treatments available. Furthermore, acne is also associated with substantial monetary outlays (1).

An increasing amount of study papers and scientific results are being published on acne treatment regimens. This is significant since there has been a tremendous amount of interest in different research achievements in this field. The aetiology and various treatment modalities of acne have been the subject of much research. Modern acne treatments have evolved to include combination approaches that target many pathologic variables simultaneously. New topical retinoids with anti-inflammatory characteristics and topical retinoids that normalise abnormal hyperkeratinization in the infundibulum are two examples of the many topical applications and treatments detailed in the most current acne treatment literature (2).

This article's goals are to provide a comprehensive overview of acne kinds, their pathophysiology, and the biochemical mechanisms behind each form of acne, as well as to examine traditional treatment pharmaceutical options in depth. The uniqueness of this study lies in its comprehensive discussion of the treatment combination and its emphasis on data from recent studies and reviews. We also made note of the dosage forms that have been effective and are now available for purchase, as well as those that are still in the trial phase. In addition, we will go over several possible clinical trial studies in depth and go over the latest advancements (3).

Factors contributing to acne pathogenies and types of acne

According to conventional wisdom, the following factors contribute to the acne vulgaris aetiology. Some of the factors that may cause or aggravate acne include heredity, environmental factors (such as pollution, humidity, temperature, and sun exposure), dietary factors, hormonal status, stress, smoking, and comedogenic medications (including androgens, halogens, corticosteroids, and bacteria). Discomfort, mental anguish, physical

disfigurement, and even scarring are common outcomes of Acne Vulgaris (AV). On top of that, patients could experience worry and shame, which add to their mental depression (Figure 1) (4).

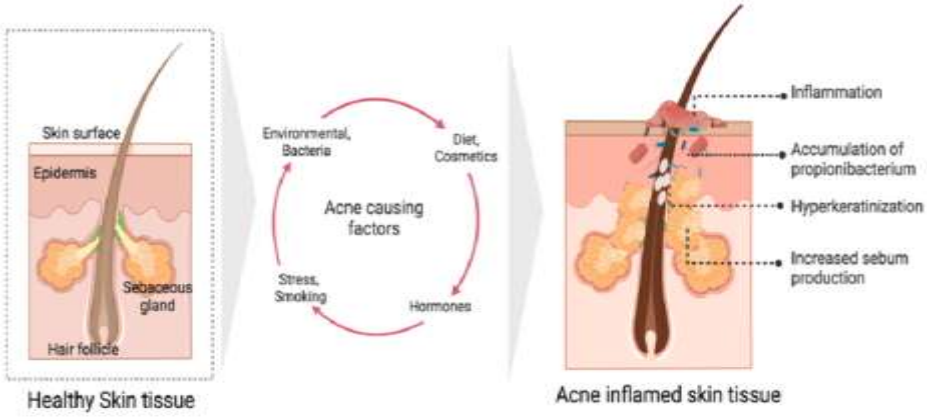

Fig. 1: Schematic illustration of healthy/normal skin tissue vs acne inflamed skin tissue, various factors (environmental, bacterial, diet, stress, smoking and relevant hormonal imbalance among others) contributing to the formation and development of acne [5]

Excepcional sebum production, abnormal hyperkeratinization of the pilosebaceous follicles, inflammatory mechanisms, and hyperproliferation of the colonising bacteria known as cutibacterium acnes (formerly propionibacterium acnes) are the four main causes of acne, which is a multifactorial disease with multiple underlying exposome factors. The pathophysiology and many contributing variables will be detailed in the section that follows (6).

Causative factors and pathogenesis of acne vulgaris

- In conventional wisdom, there are a number of potential causes of acne vulgaris. Causes of chronic acne include overproduction of sebum, abnormal keratinisation of the follicular infundibulum, inflammation brought on by bacterial infection, and endocrinological variables such androgens (7).

• Greater production of sebum

One of the major reasons why acne forms is an increase in sebum production in the hair follicles. The production and release of sebum are both boosted by androgen hormones, particularly IGH-1 and testosterone. Patients with acne vulgaris should take this into account since there is a strong association between increased sebum production and the frequency and severity of acne lesions (8). Disruptions in the normal hyperkeratinization process of the sebaceous glands In most cases, healthy follicles remove single-cell keratinocytes that have shed into the lumen. In contrast, pilosebaceous follicles get clogged with irregular desquamated corneocytes, lipids, and monofilaments when keratinocytes in acne patients overproliferate and do not drain into the lumen (9). Propionibacterium acnes (P. acnes) hyperproliferation Another agent that causes acne is Propionibacterium, which is involved in the pathophysiology of inflammatory acne to a significant degree. The gram-positive, anaerobic pathogen Cutibacterium acnes (previously propionibacterium acnes) thrives in sebaceous follicles, which are rich in sebum and provide a perfect environment for the bacterial development due to the lack of oxygen. In order to convert the triglycerides found in sebum into glycerol and fatty acids, a lipase enzyme is secreted by P. acnes. This process may cause irritation and the development of comedones on the skin (10). skin conditionInflammation starts when the immune system identifies P. acnes, which is a continuation of the previous step in the P. acne process. It is possible for P. acnes to trigger the production of chemostatic agents such as macrophages, lymphocytes, and neutrophils due to its potent inflammatory action. Furthermore, these circumstances lead to follicular injury or rupture, which in turn releases germs, lipids, and fatty acids into the dermal layer. Ulcers, pustules, nodules, cysts, and papules are inflammatory lesions that may be caused by these mechanical processes. In contrast to inflammatory lesions, non-inflammatory ones tend to be smaller and less loaded with pus. Another finding is that neutrophils are known to produce reactive oxygen species (ROS), which may harm the follicular epithelium and exacerbate inflammation in acne. Various inflammatory acne lesions are caused by the expulsion of follicular material into the dermis (11).

Protein methylation

Changes in gene expression may occur as a result of epigenetic alteration, which occurs when genes and the environment interact, when there is environmental stress. Dermatologists are paying more and more attention to DNA methylation as a mechanism of inflammatory, autoimmune, and malignant skin disorders. This is because DNA methylation is one of the epigenetic modifications that has been extensively investigated. Research

has shown that hidradenitis suppurativa, atopic dermatitis, psoriasis, and other inflammatory skin illnesses are influenced by DNA methylation. Acne vulgaris is a complex skin condition with many unknown biological processes and possible treatment options; epigenetics may shed light on these questions (12).

Acne Lesion Types

Acne comes in many different types, including cosmetica, excoriee, mechanical, medicamentosa, rosacea, acne fulminans, and acne conglobate. However, 99% of all acne instances are caused by acne vulgaris, making it the most common type of acne. Two kinds of lesions—inflammatory papules, pustules, nodules, and cysts—and non-inflammatory open and closed comedones distinguish it from another. There are two varieties of comedones: whiteheads, which are closed, and blackheads, which are open. Blackheads, whiteheads, papules, pustules, nodules, and cysts were the many kinds of lesions. (Refer to Figure 2), number 13.

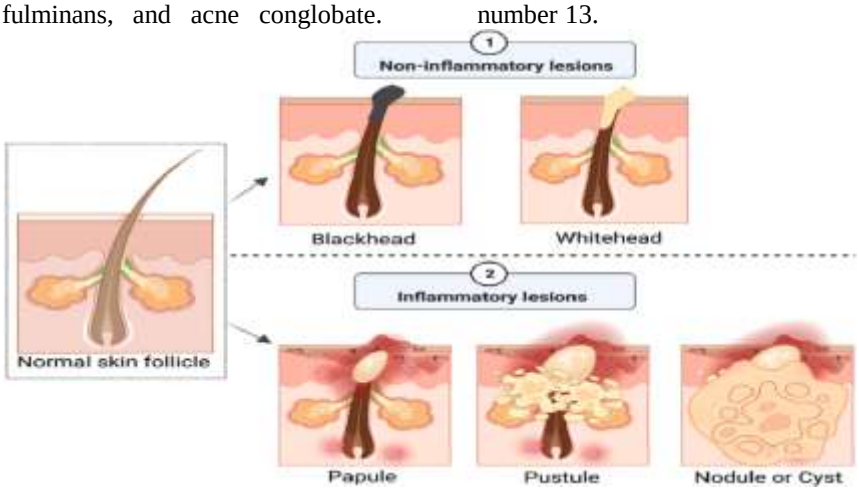

Fig. 2: Schematic illustration of major distinguishing of the two types of lesions (non-inflammatory, inflammatory) and their pathogenies [5]

Characteristics of the health

Testing for androgen levels is possible using endocrinologic assays, although it is not routine nor advised for the majority of patients. The patient's history and the presence of acne lesions in areas with a high concentration of sebum are the main diagnostic criteria instead. Although there is some variation in the lesions seen, comedones are the first sign of acne vulgaris. Comedones form when sebum and dead skin cells block the pilosebaceous follicles. When the hair follicle is completely sealed, a closed comedone forms; these are sometimes called whiteheads due to their hue. Blackheads, which are open comedones, form when oxidised melanin builds up and takes on a dark hue due to the inadequate blocking of the follicle (14).

Severity of lesions allows for classification of acne lesions into higher classes, with higher classes indicating more severe lesions (Table 1). It is important to keep in mind that acne may manifest with a variety of distinct lesions, and that these lesions can be polymorphic. While there isn't a universally accepted way to grade acne scars just yet, more accurate models include factors including the location, size, and kind of lesions. The best way to treat acne is to first determine its kind and severity (15).

Table 1: Classification of acne by type of lesions [15]

Class	Lesions present
1	Open or closed comedones (noninflammatory)
2	Pustules (inflammatory/superficial)
3	Papules (inflammatory/deep)
4	Cysts or nodules (inflammatory)

Therapeutic lines of acne vulgaris

The most common acne vulgaris treatment is as follows.

- **Using a topical agent**

When it comes to pregnant or nursing women, topical medications are often seen as safer than oral medications. There isn't often a pregnancy category for topical medications since the systemic absorption isn't thought to be important until the medicine is taken regularly or for a long time (16).

Bibromoperoxide, or BP

Some people experience mild comedolytic, keratolytic, and anti-inflammatory effects with benzoyl peroxide (BP), a powerful antibacterial medication that has been shown to kill Propionibacterium acnes by generating free radicals. For acne vulgaris, it may be used as a first-line treatment. It is common practice to mix Benzoyl peroxide with topical retinoids, which enhance its effectiveness, even if it works well on its own (17).

Antibiotics used topically

Antibacterial and recognised to have indirect anti-inflammatory effects on the skin include topical antibiotics such erythromycin and clindamycin. The use of topical clindamycin alone led to a significant increase in resistant strains as early as two months; however, a combination of topical clindamycin and 5% benzoyl peroxide did not have the same effect. Due to P. acnes resistance, clindamycin is more effective than topical erythromycin in treating acne (18).

Retinoids are cosmetic products.

To address follicular hyperkeratinization and hence prevent microcomedo development, topical retinoids, which are anti-inflammatory vitamin A compounds, are used. There is evidence that they enhance the efficacy of other oral and topical regimens. There are now three active medications on the market: adapalene, tazarotene, and tretinoin (19).

Yelaic acid

Azelaic acid 20% cream has a modest therapeutic efficacy in acne, which may be due to its properties. As a comedolytic, antimicrobial, and anti-inflammatory, it also has a little lightening effect on hyperpigmentation caused by acne. Azelaic acid has not been associated with any negative effects on the developing baby. The only other options for therapy in that group of patients are metronidazole and clindamycin, and this medicine is one of the few that fall into that category (6).

drug called dapsone

This is a sulfone that is put on the skin. Dapsone gel is an excellent therapy for mild to moderate acne, according to research. Extensive clinical research has shown that dapsone is particularly effective against inflammatory acne lesions, and that the majority of patients report improvement in their condition within one month of beginning treatment. It usually takes 2 to 3 months of therapy before non-inflammatory lesions (comedonal lesions) show signs of improvement (20).

alternatives to topical agents

There is insufficient evidence to support the administration of the following topical therapies in persons with acne. Still, niacinamide, sodium sulfacetamide, sulphur, resorcinol, aluminium chloride, topical zinc, and clinical practice have shown their efficacy (21).

Oral antibiotics and medicines

Oral antibiotics are often used for the treatment of moderate to severe inflammatory acne, as well as for inflammatory acne that does not respond to topical treatments. The oral antibiotic is best used in combination with topical retinoids and/or benzoyl peroxide rather than on its own. Avoiding long-term treatment (greater than 3 to 6 months) may help prevent the development of antibiotic resistance. To avoid this resistance, it is better to use it as a transitional treatment before moving on to other topical or oral treatments (22).

category of tetracyclines

Doxycycline and minocycline are the first-line oral antibiotics in the tetracyclines class. They are mostly known for their anti-inflammatory effects. Antibiotics of the tetracycline family, which suppress matrix metalloproteinase activity, cytokine generation, and chemotaxis in particular (23), are very useful for inflammatory acne because of their antibacterial and anti-inflammatory characteristics.

Macronides are not applicable.

Because antibiotic resistance is a worldwide problem, several authors have suggested cutting down on erythromycin use. The efficacy of azithromycin has been studied in many open-label trials with varying dosage regimens; the most common of these is pulse dosing, which is taking three to four doses of the drug monthly. One of the most common side effects of macrolides is gastrointestinal distress (24).

topical retinoin

Oral isotretinoin has a reputation for being safe and well-tolerated, despite some unfavourable social associations. In addition to treating severe cases of refractory acne vulgaris, the FDA has approved it for use in treating moderate cases of acne that are resistant to other treatments, as well as cases where acne leaves scars or causes substantial emotional or mental discomfort. Additionally, the data does not support the idea that isotretinoin use is associated with inflammatory bowel disease. Although isotretinoin is generally believed to be safe, it has clear embryotoxic and teratogenic properties (25).

Hormonal therapy

To counteract the effects of testosterone on the sebaceous gland, hormonal therapy is used. Medications such as oral contraceptives, glucocorticoids, and gonadotropin-releasing hormone (GnRH) agonists may either act as anti-androgens or inhibit the adrenal glands' or the ovary's ability to produce androgens naturally (26).

Contraceptives used orally

Acne sufferers may benefit from oral contraceptives in four key ways. The first step is a decrease in gonadal androgen production due to their restriction of LH synthesis. Two, they reduce free testosterone levels by increasing sex hormone-binding globulin synthesis. A further benefit is that they stop testosterone from being transformed into the stronger Dihydrotestosterone (DHT) by blocking the 5-alpha reductase enzyme (27).

GnRH agonists that are linked to glucocorticoids

The anti-inflammatory effects of systemic glucocorticoids, when taken at high levels, may make them useful in the treatment of acne vulgaris. Actually, they are usually saved for the worst cases, and they are often used alongside isotretinoin to

head off any potential flare-ups right from the beginning of therapy. Prolonged use of glucocorticoids increases the risk of steroid acne. Individuals who have shown androgen excess, including female patients with elevated blood Dehydroepiandrosterone (DHEAS) associated with an 11- or 21-hydroxylase insufficiency, may also benefit from short doses of glucocorticoids (28).

agents that stimulate the release of gonadotropins

GnRH agonists are effective because they interfere with the pituitary gland's cyclic secretion of gonadotropins. The end effect is a reduction in ovarian steroidogenesis in women. Ovarian hyperandrogenism is treated with these drugs. There is evidence that GnRH agonists may effectively cure hirsutism and acne in women, regardless of whether they have endocrine problems or not (29).

Conclusion:

One of the most common long-term skin conditions is acne vulgaris. Seborrhoea, blackheads, comedones, papules, pimples, and scars are the hallmarks of acne vulgaris. A number of methods exist for determining the degree of acne vulgaris, including the Leeds acne grading methodology, the Pillsbury scale, and cook's acne grading scale. Topical treatments are the gold standard for mild acne, while systemic and hormonal treatments work wonders for severe instances.

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