

A Brief Review on Acne Vulgaris: Chronic Inflammatory Disease

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Abstract: Acne vulgaris (AV) is a chronic inflammatory disease rather than a natural part of the life cycle as colloquially viewed of the pilosebaceous unit (comprising the hair follicle, hair shaft and sebaceous gland) and is among the most common dermatological conditions worldwide. Some of the key mechanisms involved in the development of acne include disturbed sebaceous gland activity associated with hyperseborrhoea (that is, increased sebum production) and alterations in sebum fatty acid composition, dysregulation of the hormone microenvironment, interaction with neuropeptides, follicular hyperkeratinization, induction of inflammation and dysfunction of the innate and adaptive immunity. Grading of acne involves lesion counting and photographic methods. However, there is a lack of consensus on the exact grading criteria, which hampers the conduction and comparison of randomized controlled clinical trials evaluating treatments. Prevention of acne relies on the successful management of modifiable risk factors, such as underlying systemic diseases and lifestyle factors. Several treatments are available, but guidelines suffer from a lack of data to make evidence-based recommendations. In addition, the complex combination treatment regimens required to target different aspects of acne pathophysiology lead to poor adherence, which undermines treatment success. Acne commonly causes scarring and reduces the quality of life of patients. New treatment options with a shift towards targeting the early processes involved in acne development instead of suppressing the effects of end products will enhance our ability to improve the outcomes for patients with acne.

Keywords: Acne Vulgaris, Chronic Inflammatory Disease.

Review Paper

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INTRODUCTION

Acne vulgaris (AV) is a disease of the pilosebaceous unit that causes noninflammatory lesions (open and closed comedones), inflammatory lesions (papules, pustules, and nodules), and varying degrees of scarring. AV is an extremely common condition with a lifetime prevalence of approximately 85% and occurs mostly during adolescence [1]. AV can persist into adult-hood, with a 50.9% prevalence rate of acne in women ages 20 to 29 years versus 26.3% in women ages 40 to 49 years [2]. Female patients account for two thirds of visits made to dermatologists for acne, and one third of all dermatology office visits for acne are by women who are older than 25 years [3].

Acne leads to significant morbidity that is associated with residual scarring and psychological disturbances such as poor self-image, depression, and anxiety, which leads to a negative impact on quality of life [4-6]. In one epidemiologic study by Yentzer *et al.*,

(2010) [3], 8.8% of patients with acne reported depression with women suffering from depression twice as often as men (10.6% vs. 5.3%), but this was unrelated to acne severity.

SYMPTOMS:

Acne vulgaris (or simply acne) is characterized by [7]:

- areas of seborrhea (scaly red skin),
- comedones (blackheads and whiteheads),
- papules (pinheads), nodules (large papules),
- pimples and ultimately scarring.

Other symptoms may include pain, tenderness or erythema depending upon the severity of disease. Systemic symptoms are most often absent in acne vulgaris. Severe acne with associated systemic signs and symptoms, such as fever, is referred to as acne fulminans. Severe acne, characterized by multiple comedones, without the presence of systemic symptoms, is known as acne conglobata. This severe form of acne frequently heals with disfiguring

scars. Moreover, acne has a psychological impact depending on the severity or grade of the disease [8].

CAUSES OF ACNE:

Acne appears mostly in young people due to several factors [9]

- **Hormonal imbalances** (overproduction of the male sex hormones)

Menstrual cycles and puberty may also cause acne. During puberty, an increase in androgen levels causes the enlargement of follicular glands and sebum production is also increased [10, 11]. Anabolic steroids produce a similar effect [12]. Several hormones are linked with acne, like testosterone, dihydrotestosterone, dehydroepiandrosterone sulfate and insulin-like growth factor 1 (IGF-I). In later years, the development of acne vulgaris is uncommon but rosacea incidence will increase, which is having similar symptoms in older age groups. Acne vulgaris in adult women may be due to an underlying condition such as pregnancy, Cushing's syndrome, hirsutism or polycystic ovary syndrome. Acne climacterica refers to menopause-associated acne, occurs as a result of the anti-acne, ovarian hormone estradiol and progesterone allowing the acne-causing hormone testosterone to continuously exert its effects.

- **Bacterial infection:**

Propionibacterium acnes (*P. acnes*) are anaerobic bacterial species that mainly cause acne. *Staphylococcus aureus* has been discovered to play an important role since normal pores are colonized only by *Propionibacterium acnes* [13]. Specific clonal sub-strains of *P. acnes* are also associated with normal skin health and long-term acne problems. These strains have the capability of changing, perpetuating or adapting to the abnormal cycle of inflammation, oil production and inadequate sloughing activities of acne pores. For at least 87 years, one virulent strain of *Propionibacterium acnes* has been circulating around Europe [14]. Antibiotic resistance has been continuously increasing to *P. acnes* in vitro [15].

- **Heredity or genetics**

The genetics of acne susceptibility is polygenic as the disease does not follow a classic Mendelian inheritance pattern.

- Consumption of certain drugs (including androgens and barbiturates)

Drugs like Phenytoin, Isoniazid, Phenobarbital, Lithium, Ethionamide, Steroids, Azathioprine, Quinine and Rifampin cause acne [16].

- **Exposure to environmental irritants** (such as pollution and high humidity)

It includes various factors like high humidity, prolonged sweating, increase in skin hydration,

exposure to dirt or vaporized cooking oil or certain chemicals like petroleum derivatives.

- Stress
- Cosmetic application
- Hard scrubbing of the skin

An increase in hormonal activity, especially during puberty, may cause the formation of acne. The most important cause attributed is infection due to *Propionibacterium acnes* (*P. acnes*), the anaerobic bacterial species [1].

DIAGNOSIS AND EVALUATION

The diagnosis of AV is generally established by identifying the quantity and morphology of the lesions. Their morphologies are divided into the non-inflammatory comedones, termed as open (blackheads) or closed (whiteheads) and the inflammatory lesions, termed as papules, pustules, cysts, or nodules.

The American Academy of Dermatology (AAD) classified the severity of AV into mild, moderate, and severe. Mild AV is characterized by the presence of a few to several papules and pustules, but no nodules. Moderate AV is characterized by several papules and pustules, along with a few nodules. Severe AV is characterized by numerous or extensive papules and pustules, as well as multiple nodules [17].

DIFFERENTIAL DIAGNOSIS

There are several differential diagnoses of AV, such as (1) acne rosacea, which is commonly observed in middle age or later in life, (2) folliculitis and boils, which often present with pustular lesions similar to acne, (3) milia, which is a small non-follicular keratin papule that may be confused with whiteheads, and (4) pityrosporum folliculitis, which more predominates on the trunk [18].

MEDICATION: TOPICAL THERAPIES

Topical therapies are considered one of the mainstay treatments for patients with mild-to-moderate acne [19]. These topical agents are available over the counter and by prescription. More recently, several topical therapy combinations have been developed to treat patients with acne. The absorption of topical therapies is influenced by many factors, including the amount of agent applied, surface area of the application, length of the application time, frequency of the application, application to broken skin/erosions, choice of vehicle used, and thickness of the stratum corneum [20].

Commonly used topical treatments for patients with acne include benzoyl peroxide (BP), salicylic acid (SA), antibiotic medications, combination antibiotic medications with BP, retinoid medications, retinoid

with BP, retinoid with antibiotic medication, azelaic acid, and sulfone agents [21].

BENZOYL PEROXIDE

BP is commonly used to treat patients with acne and is available in a variety of strengths (2.5-10%) and formulations (cream, gel, wash, foam, aqueous gel, leave-on, and wash-off). BP is a comedolytic, keratolytic, anti-inflammatory agent with antimicrobial properties. BP is bactericidal mainly against *P. acnes* by the production of reactive oxygen radicals and has not developed resistance [22]. The addition of BP to antibiotic therapy enhances results and may reduce antibiotic resistance development [21]. Topical BP in varying formulations may be used 1 to 3 times daily as tolerated.

SALICYLIC ACID

SA is a comedolytic agent that is available over the counter in 0.5 to 2% strengths and in both wash-off and leave-on preparations. SA is generally well tolerated by patients, but its efficacy in acne is limited [23]. BP and SA are the most widely used over-the-counter, topical, acne treatments and are often used in combination. SA may be applied 1 to 3 times daily as tolerated. SA has an FDA pregnancy rating of C.

TOPICAL ANTIBIOTIC MEDICATIONS

Topical antibiotic medications are thought to accumulate in the follicle and may work through both anti-inflammatory and antibacterial effects [24]. Due to increasing antibiotic resistance, monotherapy with topical antibiotic medications in the management of acne is not recommended. Topical antibiotic medications are best used in combination with BP [21]. The main topical antibiotic medications are clindamycin and erythromycin.

TOPICAL CLINDAMYCIN

Clindamycin is available in a gel, lotion, pledget, or topical solution and has been assigned FDA pregnancy category B. The clindamycin 1% solution or gel is currently the preferred topical antibiotic medication [25]. The recommended dosing is an application of a thin layer once daily.

TOPICAL ERYTHROMYCIN

Erythromycin is available as a gel, solution, ointment, pledget, or thin film. Oral and topical erythromycin formulations are both classified as FDA category B. Topical erythromycin is less efficacious in patients with acne than clindamycin because of *P. acnes* resistance [23, 24, 26-28]. Stable, fixed-combination agents are available with erythromycin 3% plus BP 5%, clindamycin 1% plus BP 5%, and clindamycin 1% plus BP 3.75% [29-31]. Combination agents may enhance compliance with treatment

regimens [21]. Topical erythromycin is usually administered 1 to 2 times daily.

TOPICAL RETINOID MEDICATIONS

Topical retinoid medications are vitamin A-derivative prescription agents [23, 32-34]. Topical retinoid medications are often used as first-line treatment for patients with mild-to-moderate acne, especially when the acne is mainly comedonal. Retinoid therapy is comedolytic and resolves the precursor microcomedone lesion. Retinoid medications are also anti-inflammatory and work in combination with other topical agents for all acne variants [21]. Topical retinoid treatments are the mainstay in the maintenance of clearance after discontinuation of oral therapy [21]. The recommended dosing is application of a thin layer once daily.

AZELAIC ACID

Azelaic acid acts as a comedolytic, antimicrobial, and anti-inflammatory agent [35] and is a naturally occurring dicarboxylic acid that is found in whole-grain cereals such as wheat, rye, and barley [36]. Azelaic acid should be used with caution in patients with sensitive skin due to side effects that include redness, burning, and irritation.

Azelaic acid should also be used with caution in patients with Fitzpatrick skin types IV or greater because of its potential lightening effect [37-39]. However, because of this side effect, azelaic acid is a useful adjunctive in acne treatment because it aids in the treatment of post inflammatory dyspigmentation.

DAPSONE

Dapsone is a sulfone agent that is available in a 5% gel and used as a twice-daily agent or 7.5% gel used once daily. Data only show modest-to-moderate efficacy in the reduction of inflammatory acne lesions [34, 40]. Dapsone has a poorly understood mechanism in the treatment of patients with acne and its ability to kill *P. acnes* has been studied poorly [21]. Similar to other topical antibiotic treatments, dapsone is thought to work as an anti-inflammatory agent. The recommended dosing is application of a thin layer twice daily.

OTHER TOPICAL AGENTS

The following topical agents lack evidence-based data for their use in patients with acne but have been demonstrated to be effective in clinical practice: sodium sulfacetamide [41-43], sulfur [44], resorcinol [44], aluminum chloride [45, 46], topical zinc [47, 48], and niacinamide [23, 49].

CONCLUSION

Although acne is a very common and costly disease, it does not receive the attention it deserves. Acne was among the under-represented diseases in

Cochrane Database of Systematic Reviews when matched with corresponding diseases with a similar burden defined by disability-adjusted life years from the Global Burden of Disease 2010 project¹. Another study showed that although acne caused the fourth greatest skin-related disability in the United States, it received less than half of the funding that was given by National Institute of Arthritis and Musculoskeletal and Skin Diseases to projects on bacterial skin diseases, which only rank thirteenth on the disability score. To advance the understanding and treatment of acne, one first needs to acknowledge that it is an important problem. Basic research is needed to define pathways and regulatory nodes that can potentially be targeted to prevent and treat acne and requires a multidisciplinary approach, including microbiology, endocrinology, immunology, genetics and dermatology. On the basis of the results obtained from these research projects, new therapeutic agents have been developed or are under development. Formulation of consensus guidelines requires large, well designed, comparative, randomized controlled trials.

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