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ACNE VULGARIS: PATHOPHYSIOLOGY, CLINICAL MANAGEMENT, AND EMERGING THERAPEUTIC STRATEGIES

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ABSTRACT

Acne vulgaris is one of the most common dermatological disorders, affecting approximately 85% of adolescents and a significant number of adults. It is a multifactorial disease characterized by the interaction of increased sebum production, follicular hyperkeratinization, *Cutibacterium acnes* colonization, and inflammation. This review provides a comprehensive overview of the pathophysiology, classification, and clinical presentation of acne, while highlighting current treatment strategies including topical agents, systemic therapies, hormonal treatments, and novel therapeutic approaches such as light-based technologies and phytotherapy. Special emphasis is placed on emerging therapies and the growing concern of antibiotic resistance. Furthermore, the psychosocial impact of acne and the importance of individualized, evidence-based treatment plans are discussed. Advancements in acne research continue to evolve, offering promising alternatives to traditional therapy and improving patient outcomes.

KEYWORD: Acne vulgaris, Propionibacterium, Pathophysiology, Clinical Characteristics, Diagnosis, Treatment.

INTRODUCTION

Acne vulgaris ranks among the most widespread dermatological issues globally, impacting as many as 85% of adolescents and young adults. Although it is frequently regarded as a mild and self-limiting condition, acne can have significant psychological and emotional repercussions, particularly during the crucial adolescent phase. The implications of acne extend beyond mere skin issues, often resulting in reduced self-esteem, social withdrawal, anxiety, and depression for many individuals.

This chronic inflammatory condition affects the pilosebaceous units, mainly on the face, chest, and back. It usually presents with a variety of lesions, including non-inflammatory types like open (Blackheads) and closed (Whiteheads) comedones, as well as inflammatory types such as papules, pustules, nodules, and cysts. In more severe or untreated cases, these lesions can lead to permanent scarring and alterations in skin pigmentation.

Acne management, while common, can be quite complicated. Patients and healthcare providers are often faced with a wide range of treatment options, including topical therapies, oral medications, and various adjunctive treatments. Choosing the right approach requires a careful evaluation of the type and severity of acne, as well as the patient's age, skin type, and psychosocial factors. This review aims to offer a structured and practical method for managing acne vulgaris. We will explore its pathophysiology, outline clinical assessment strategies, review current topical and systemic treatments, and discuss emerging therapeutic options. By synthesizing the latest evidence and clinical guidelines, this article aspires to assist clinicians in providing effective and individualized care for those affected by acne.

Impact of acne: Psychosocial Burden and Quality of Life

Acne vulgaris transcends mere physical symptoms, imposing a considerable psychosocial burden that can detrimentally influence patients' self-esteem, body image, and emotional health. The visibility of acne lesions, particularly on the face, often triggers feelings of embarrassment, social withdrawal, and a decline in self-confidence, especially among adolescents and young adults who are navigating intricate emotional and social developmental phases.[1] Research has shown that the psychological ramifications of acne can be comparable to those experienced with chronic conditions such as asthma, diabetes, and epilepsy.[2] Acne is associated with increased anxiety, depression, and even suicidal thoughts, particularly in severe or treatment-resistant cases.[3,4] Furthermore, the impact on quality of life

(QoL) is not always directly related to the severity of acne; even mild cases can significantly affect a patient's psychological state if they are perceived as distressing. Tools like the Dermatology Life Quality Index (DLQI) and the Acne-Specific Quality of Life Questionnaire (Acne-QoL) are commonly employed to measure this burden in both clinical practice and research.[5]

Purpose and Scope of the review

The purpose of this review is to present a detailed and clinically significant overview of acne vulgaris. It covers the current insights into the pathophysiology of the condition, outlines its clinical features and classifications, and reviews the treatment alternatives, including topical and systemic therapies.[5] Furthermore, the review points out innovative treatment approaches and research trends that may impact future clinical practices. The aim is to equip healthcare professionals with a structured, evidence-based methodology for the diagnosis and management of acne across diverse patient groups and severity ranges.[6]

What causes acne?

Acne is characterized as an inflammatory disorder of the pilosebaceous duct, stemming from four key pathophysiological processes:

- Abnormal keratinocyte growth and shedding, which causes ductal blockage
- An increase in sebum production driven by androgens
- The proliferation of Propionibacterium acnes
- Inflammatory responses.

When androgen levels rise, they trigger irregular keratinocyte shedding and follicular occlusion, leading to the formation of the microcomedone—the initial subclinical lesion in acne. Although microcomedones are not detectable during clinical evaluations, they can develop into visible lesions. Furthermore, elevated androgen levels boost the activity of sebaceous glands, resulting in excessive sebum production. The combination of sebum buildup and follicular blockage leads to the emergence of both open (Blackheads) and closed comedones (Whiteheads). The sebum provides a favorable environment for the growth of Cutibacterium acnes (Formerly Propionibacterium acnes). This overgrowth of bacteria triggers the release of pro-inflammatory mediators, and the subsequent rupture of follicles worsens inflammation by releasing their contents into the surrounding dermis.[7]

The inflammatory response is responsible for the emergence of papules, pustules, nodules, and cysts, which are defining characteristics of inflammatory acne. Successful treatment necessitates a deep comprehension of the four main pathogenic mechanisms that play a role in acne development. Healthcare providers should adapt their therapeutic approaches based on the prevalent lesion types, implementing treatments that focus on the unique underlying pathophysiological factors for each patient.[8,9,10]

Characteristics of cutaneous propionibacteria

The species of *Propionibacterium* that inhabit the skin, now reclassified as *Cutibacterium,* consist of *Cutibacterium acnes* (Previously known as P. acnes), *P. avidum, P. granulosum, P. propionicum*, and *P. lymphophilum.* These microorganisms are typically regarded as commensals of human skin and other keratinized epithelial tissues. Historically, they have been inaccurately categorized under various genera, such as Bacillus, *Corynebacterium*, *anaerobic diphtheroids*, and *Propionibacterium* which is a consideration for interpreting earlier studies.[11]

Morphologically, they are gram-positive, non-motile rods with a coryneform (club-shaped) appearance and frequently exhibit short, irregular branches under microscope. Although such organisms are neither completely anaerobic or lipophilic in nature they grow best in anaerobic environments at 35°C on Tween 80-supplemented medium.[12]

P. acnes and P. granulosum are often isolated from sebaceous, oil-rich parts of the body, such as the face, chest, and back, where they reside in pilosebaceous follicles.[13,14] In contrast, P. avidum prefers to colonise the axillary areas.[15] P. propionicum and P. lymphophilum are still poorly understood organisms. Furthermore, a sixth strain previously identified as P. innocuum has been reclassified as Propioniferax innocua.[16]

Pathophysiology of acne vulgaris

Acne vulgaris results from a complex combination of biological processes within pilosebaceous units, which are made up of hair follicles and sebaceous glands. Acne lesions are caused by four main processes.[17,18]

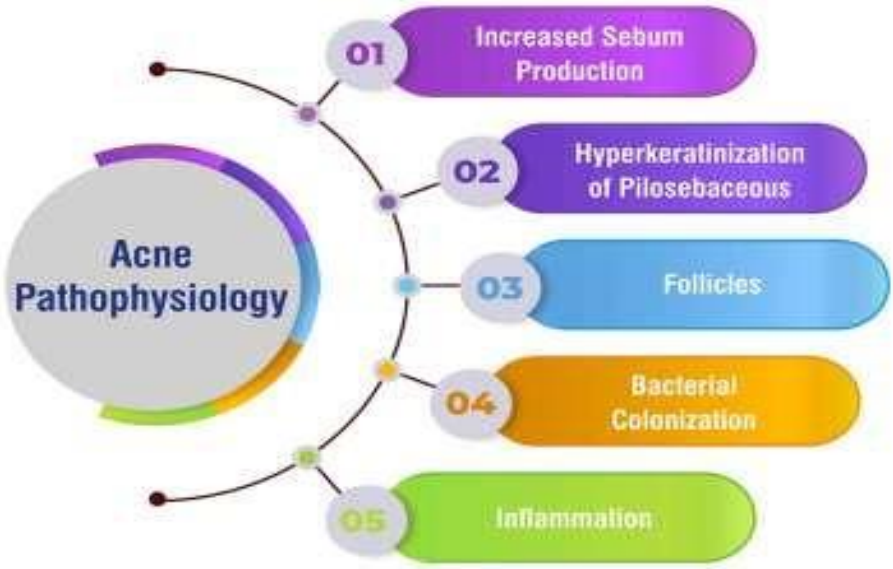

Fig. no. 1: Pathophysiology of acne.

1. Excess sebum production

During puberty and adolescence, androgen hormones, notably dihydrotestosterone (DHT), cause the sebaceous glands to generate more oils. This increased sebum secretion causes pore obstruction and generates a lipid-rich environment that promotes bacteria development. Variations in the content of oil can also cause local irritation.

2. Follicular hyperkeratinisation

Acne disrupts the regular exfoliation of keratinocytes in the follicular lining. This causes an accumulation of cell debris, which, when mixed with sebum, produce a clog that blocks the follicle. These first microcomedones are the first observable lesions in acne formation.

3. Bacterial colonisation

The clogged pores create a perfect anaerobic habitat for Cutibacterium acnes (C. acnes), a commensal bacterium that flourishes in sebaceous regions of the dermis. As microbes grow, they produce enzymes and pro-inflammatory cytokines, which activate the immune system and contribute to the advancement of swelling.

4. Inflammatory response

The immune response to antigens of bacteria and sebum components causes the recruitment of cells that are inflammatory such as neutrophils and macrophages. In clinical terms, this inflammation appears as papules, pustules, nodules, or cysts, depending on the degree. Long or significant inflammation may cause post-inflammatory hyperpigmentation or irreversible scars.

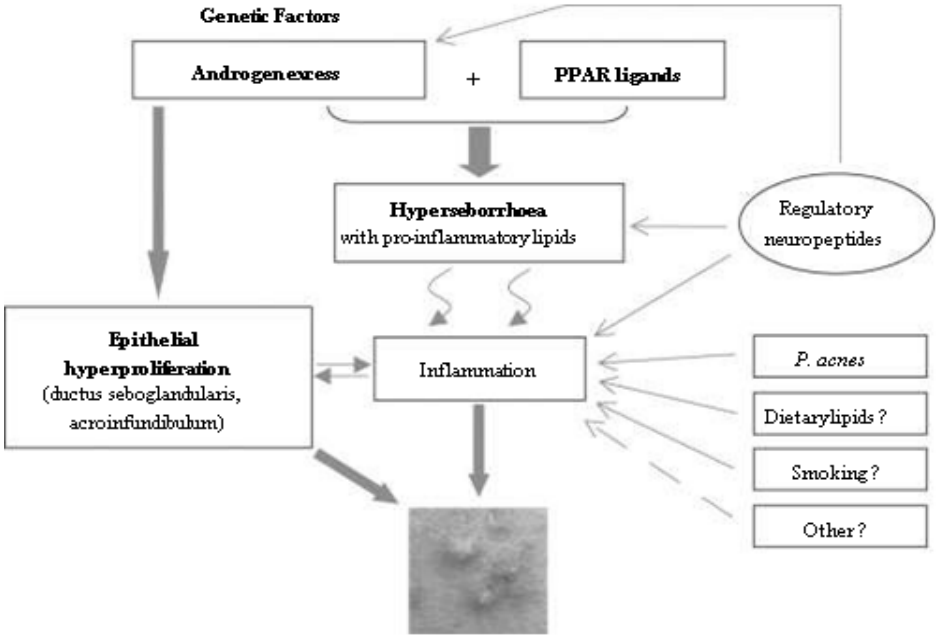

Fig. no. 2: Natural cycling of the sebaceous follicle (Microcomedone).

Imbalanced stimulation or poor negative feedback systems can lead to the development of medically visible acne lesions such as comedones and inflammation papules. Changes in diet are additionally associated with the growth of acne. Diets from the West in particular, which are heavy in pro-inflammatory omega-6 and trans fats and deficient in omega-3 fatty acids and antioxidant vitamins, have been linked to an increase in acne prevalence. Particularly, the omega-6 to omega-3 fatty acid ratio in Western diets is around 20:1, as opposed to the more balanced 1:1 ratio reported in conventional dietary habits.[19,20,21]

Although the impact of nutrition on acne remains contested, data from population studies has piqued attention. One research found that acne does not occur with the Kitavan islanders of Papua New Guinea or the Ache hunter-gatherers of Paraguay, both of whom eat conventional non-Westernized diets.[22] However, some studies have suggested that these findings may be due to genetic or environment variances instead of dietary variables.[23]

Classification of acne vulgaris

Acne vulgaris can be characterised according to lesion type, severity, and age of occurrence. Proper categorisation is essential for directing treatment options and determining prognosis. The categorisation often falls into the following categories:[24,25]

1. Morphological classification (Lesion types)

Acne may be roughly classified into two major categories depending on the prominent lesions.

Non-inflammatory acne

Blackheads (Open comedones)

Whiteheads (Closed comedones)

Acne papules (Inflammatory) Pustules, nodules, and cysts.

2. Severity-based classification

Severity is often determined by lesion kind, quantity, and distribution. Typical systems include the following:

- Mild acne is characterised by non-inflammatory pimples with a few inflammatory papules or pustules.
- Moderate acne consists of breakouts and inflammatory lesions, with probable trunk involvement.
- Severe acne causes many inflammatory lesions, such as nodules and cysts, with a significant risk of scars.

Grading systems, such as the Global Acne Grading System (GAGS) and the Leeds Method, are often employed in both clinical and academic settings to objectively evaluate severity.[26,27,28]

3. Special forms based on age or aetiology

- Newborn acne appears within the first few weeks of life and is normally self-limiting.
- Infantile acne typically lasts 3-6 months and might need treatment to prevent scarring.
- Adult acne (Acne tarda) is typically more chronic and inflammatory in those over the age of 25.
- Acne fulminans is a rare, severe, ulcerative acne that causes systemic symptoms.
- Acne conglobata is a severe, chronic variant with linked nodules and cysts, resulting in scarring.

Clinical characteristics of acne vulgaris

Acne vulgaris is a chronic inflammatory skin illness that causes a variety of lesions, which are classed as non-inflammatory or inflammation. Open and closed comedones (blackheads and whiteheads) are non-inflammatory lesions caused by follicular plugging. Inflammatory lesions include papules, pustules, nodules, and cysts, which are frequently accompanied by erythema, discomfort, and an increased risk of scars. They usually appear in locations with a high density of sebaceous glands, such as the skin of the face, chest area, back, and upper shoulder.[29,30]

The presence of comedones is required to diagnose acne vulgaris. If comedones are not present, doctors should look for acneiform conditions that might cause acne, such as rosacea, folliculitis, perioral dermatitis, angiofibromas, and keratosis pilaris.[31]

Age-associated characteristics can also help differentiate acne from other dermatological diseases. Keratosis pilaris and perioral dermatitis, for example, are more frequent in youngsters, but rosacea is generally encountered in people over the age of 30. In situations when the diagnosis is unclear or the appearance is unusual, a dermatologist should be consulted for additional assessment.[32]

Peripheral hyperandrogenism in acne

Women with peripheral hyperandrogenism commonly describe premenstrual acne flare-ups, which are associated by moderate increases in dehydroepiandrosterone (DHEA) levels and elevated anti-Müllerian hormone (AMH), despite otherwise normal serum androgen profiles. Clinical indications may include the appearance of small vellus hairs on the upper lip, periorbital regions, and cheeks, indicating a modest androgenic impact on the skin.[33,34]

Evidence for peripheral hyperandrogenism received more attention following the French Health Agency's 2012 suggestion to prioritise second-generation oral contraceptives (OCs) over third-generation choices due to concerns about thromboembolic events. This regulatory change, introduced in 2013, has dermatological implications. A French multicenter survey done a year following the guideline modification revealed that 83.9% of the individuals who switched to second-generation OCs had worsening acne, supporting the relationship between peripheral hyperandrogenism and acne pathogenesis.[35]

These results sparked interest in anti-androgen treatments, notably spironolactone, as a substitute to isotretinoin in treating hormonally driven acne. While the FDA and EMA have not authorised spironolactone for acne therapy, it has showed promise due to its ability to inhibit androgen receptors, lower sebaceous gland action, and diminish androgen-dependent hair growth.[36] A small-scale trial of 16 women treated with oral spironolactone (75-150 mg/day) in conjunction with a third-generation OC and either topically benzoyl peroxide 0.25% or a topically applied retinoid showed substantial clinical improvements in acne lesions at 6 and 12 months.[37] In recent years, the creation of topical spironolactone formulations that are such as solid lipid nanoparticles that has shown the ability to improve skin distribution while lowering systemic adverse effects. However, bigger controlled trials are needed to determine the efficacy and security of these new formulations.[38]

Data Collection and Statistical Analysis

This retrospective series of cases was carried out in our multi-institutional centre, with ethical authorisation and institutional review board clearance. The Medical Archival Retrieval System (MARS) was used to extract data from 7,000 people receiving dialysis between January 2000 and December 2013, containing clinical information, lab results, and peripheral smear findings.

Complete blood counts (CBCs) were done on EDTA-anticoagulated samples using a Beckman-Coulter DXH analyser. Only the lowest platelet levels were examined, omitting those with obvious confounding factors.

A Stago Star Evolution analyser was used to evaluate coagulation parameters, including prothrombin time (PT) and activated partial thromboplastin time (aPTT). Results obtained within six hours after treatment were removed to prevent anticoagulant-related artefacts.

Patients who had peripheral smear tests prior to and following dialysis and gathered demographic information (age, gender, and race). Variables tested were WBC and granulocyte counts, thrombocytopenia/thrombocytosis, and abnormalities in coagulation.

Individuals with diseases that cause red cell fragmentation (such as DIC, TTP/HUS, vasculitis, malignant hypertension, and vascular devices) were excluded. Haematology technicians used 100x oil immersion to detect fragmented red cells (helmet cells, triangulocytes, pre-keratocytes) according to ICSH criteria.[39]

Diagnostic approaches for acne vulgaris

Acne vulgaris is generally diagnosed clinically, with a detailed history and physical examination. Diagnostic techniques seek to determine the kind, location, and intensity of lesions while excluding out other dermatoses that may resemble acne.

1. Clinical evaluation.

- Acne lesions include both non-inflammatory (Open and Closed comedones) and inflammatory (Papules, pustules, nodules, cysts).[40]
- Lesions primarily affect sebaceous-rich regions, including the face, chest, and back.[41]

- **Grading severity**

Mild: Mostly comedones with minor inflammatory lesions.
Moderate: Skin conditions include comedones and inflammation.
Severe cases: Include nodules, cysts, and scarring.[42]

2. Patient history

A comprehensive history includes:

- Age of onset and duration
- Cyclical flares (Especially in females)
- Aggravating factors (Stress, Cosmetics, Diet)
- Previous treatments and outcomes
- Family history of acne.[40,41,42,43]

3. Differential diagnosis

Conditions that mimic acne but lack comedones should be considered:

- **Rosacea:** Presents with flushing and telangiectasias; no comedones.
- **Perioral dermatitis:** Erythematous papules around the mouth; often steroid-induced.
- **Folliculitis:** Involves pustules and hair follicles.
- **Keratosis pilaris:** Appears on extensor arms and thighs; rough keratotic papules. Age of onset and morphology help distinguish these conditions.[41-45]

4. Hormonal Assessment (if indicated)

Testing may be warranted in females with:

- Irregular menses
- Hirsutism
- Sudden-onset or refractory can

Suggested tests

- Total and free testosterone
- DHEAS
- LH/FSH ratio
- Anti-Müllerian hormone (AMH)
- Pelvic ultrasound to evaluate for polycystic ovaries.[46,47]

5. Use of Photographs

Standardized clinical photography aids in assessing disease progression and response to therapy, especially in moderate-to-severe cases.[42]

6. Specialist referral

Referral to a dermatologist is appropriate when:

- Diagnosis is uncertain
- Severe or nodulocystic acne is present
- Acne is unresponsive to conventional treatment
- There is significant psychosocial impact or scarring.[40,41]

Treatment for acne vulgaris

Acne vulgaris therapy is adapted to the intensity and kind of lesions (Comedonal, inflammatory, or nodulocystic), as well as the patient's age, skin type, and psychological status. Topical, systemic, and procedural therapy may be used to manage this condition. Because acne is a complex disease, combination therapies are frequently more successful.

1. Topical therapies

Comedolytic, antimicrobial, and anti-inflammatory medicines are common topical treatments used to treat mild to moderate acne.

- Topical retinoids improve desquamation and minimise microcomedone development. Frequent agents include tretinoin, adapalene, and tazarotene. They work well for both comedonal and inflammatory acne and are frequently used as the foundation of topical regimens.[47,48]
- Benzoyl Peroxide (BPO) is an antibacterial and keratolytic agent that decreases Cutibacterium acnes growth and irritation. Frequently used in conjunction with topical antibiotics to avoid resistance.[49]
- Topical antibiotics like clindamycin and erythromycin are used to treat inflammatory lesions. Because of resistance issues, they are seldom used as monotherapy.[50]
- Azelaic Acid has antibacterial and anti-inflammatory effects, making it ideal for sensitive skin and post-inflammatory hyperpigmentation.[51]

2. Systemic therapies

Systemic therapies are used for moderate to severe acne, nodulocystic acne, or when topical treatments have failed.

- Tetracyclines, such as doxycycline and minocycline, are commonly used as first-line systemic antibiotics due to their anti-inflammatory properties. When tetracyclines are not an option, macrolides can be used instead. Long-term usage should be avoided to decrease resistance.[52]
- Hormonal Therapy: Effective for women with hyperandrogenism or hormonal acne.
- Combined oral contraceptives (COCs) reduce sebum production by reducing testosterone levels.[53]
- Spironolactone, an off-label anti-androgen medication, has been shown to effectively treat resistant acne in women.[54]
- Oral Isotretinoin: Reserved for severe nodulocystic acne or acne unresponsive to other treatments. It targets all four major acne pathophysiologic factors and can induce longterm remission. Requires monitoring due to teratogenicity and potential adverse effects.[55]

3. Procedural therapies

Adjunctive or alternative therapies, particularly for patients who do not react to pharmacological therapy.

- Chemical peels, such as salicylic or glycollic acid, can remove comedones and improve the appearance of skin.[56]
- Blue light, pulsed dye lasers, and photodynamic treatment can effectively treat C. acnes and inflammation.[57]
- Extraction and corticosteroid injections can alleviate inflammation and scarring in cystic lesions.[58]

4. Developing and Adjunctive therapies

- Topical Dapsone has anti-inflammatory properties and is beneficial for adult female acne.[59]

Probiotics and Diet Modification: Evidence supports its use as an adjuvant treatment, particularly in individuals with suspected diet-related flares.[60]

Antibiotic Resistance and Challenges in acne treatment

1. Emergence of resistance

Antibiotics have been a cornerstone in acne therapy for decades due to their antiinflammatory and antimicrobial effects, particularly targeting Cutibacterium acnes (formerly Propionibacterium acnes). However, the widespread and prolonged use of antibiotics— especially when used as monotherapy—has led to a significant increase in antibiotic-resistant strains of C. acnes globally.

- Studies have shown that resistance to commonly used antibiotics such as clindamycin, erythromycin, and tetracyclines is becoming increasingly prevalent.[61]
- Resistance not only reduces treatment efficacy but may also impact the skin microbiome and contribute to broader public health concerns by fostering multidrugresistant organisms.[62]

2. Clinical implications

The development of resistance compromises the effectiveness of standard therapies and may lead to:

- Treatment failure and prolonged disease course
- Increased inflammation and risk of scarring
- Cross-resistance, particularly with erythromycin and clindamycin, due to shared mechanisms of action
- Need for alternative or adjunctive therapies, often more costly or with a higher side effect profile.[63]

3. Strategies for mitigating resistance

Recent guidelines emphasise four critical techniques for addressing and preventing antibiotic resistance in acne management:

- To reduce resistance, mix antibiotics with benzoyl peroxide or a topical retinoid rather to using them alone.[64]
- Limit the duration of systemic antibiotics. Long-term usage (more than three to four months) is discouraged. Regular reassessments of need are advised.
- Use non-antibiotic options such as benzoyl peroxide, retinoids, azelaic acid, hormone treatments, or

light/laser therapy, particularly during the maintenance period.[65]
- Encourage patients to stick to combination therapy and avoid self-medication or premature withdrawal.

4. Global Surveillance and Resistance Patterns

Antibiotic resistance rates vary by area, yet they are continually increasing:
- Some places in Europe and Asia have over 50% resistance to erythromycin and clindamycin, according to research.[66]

In the US, resistance to topical antibiotics is more likely due to incorrect or extended usage without supplementary medicines.[67]

A 2020 comprehensive review found a global resistance rate to C. acnes of 20-60%, emphasising the importance of stewardship and personalised therapy based on local resistance patterns.[68]

5. Future Challenges and Directions

Microbiome-targeted treatments and phage therapy are being studied to deliver antibacterial effect without affecting normal skin flora.[69]
- Vaccines against C. acnes are now under preclinical testing.[70]
- Improved diagnostic technologies for detecting resistance patterns can inform personalised treatment options.

CONCLUSION

Acne vulgaris is not only a widespread dermatologic condition but also a multifactorial disease with profound clinical and psychosocial consequences. Effective management requires a thorough understanding of its pathophysiology—highlighting the interplay between follicular hyperkeratinization, excess sebum production, *Cutibacterium acnes* colonization, and inflammation.

From a clinical standpoint, the selection of therapy should be tailored to the severity and type of lesions, with an emphasis on combination regimens that reduce the risk of resistance and enhance treatment efficacy. However, the rising concern over antibiotic resistance underscores the need for judicious use of antimicrobial agents and consideration of nonantibiotic alternatives such as retinoids, hormonal therapies, and newer topical agents like clascoterone and dapsone. The psychosocial burden of acne—particularly among adolescents and young adults—should not be underestimated. Depression, anxiety, and diminished self-esteem often accompany persistent or severe cases, highlighting the importance of early intervention and holistic care approaches that address both physical and emotional well-being.

Looking ahead, research into individualized therapies, microbiome modulation, and hormonal pathways will play a critical role in improving outcomes. Clinicians must stay informed about evolving guidelines, resistance patterns, and patient-centered strategies to provide optimal and empathetic care.

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