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Cutibacterium acnes and Acne Vulgaris: A Narrative Review of Epidemiology, Pathogenesis, Diagnosis, Management, and Future Perspectives

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Abstract

Background and Aims: Acne vulgaris is among the most prevalent inflammatory skin disorders worldwide and represents a substantial source of dermatologic morbidity and psychosocial distress, particularly among adolescents and young adults. This narrative review aimed to synthesize contemporary evidence on the epidemiology, molecular microbiology, pathogenesis, clinical diagnosis, management, prevention, and psychosocial burden of acne vulgaris, while also examining unresolved questions and emerging concepts that may inform future therapeutic strategies.

Methods: The review was conducted in accordance with the principles of the SANRA (Scale for the Assessment of Narrative Review Articles). A structured literature search was performed in PubMed/MEDLINE to identify the relevant publications addressing the microbiology of *Cutibacterium acnes*, the pathogenesis, epidemiology, diagnosis, management, prevention, and psychosocial impact of acne vulgaris with the search concluding on 1 March 2026.

Results: Acne vulgaris arises from a multifactorial disruption of the pilosebaceous unit involving increased sebum production, follicular hyper-keratinization, microbiome alterations, and dysregulated immune responses. Disease expression reflects bacterial overgrowth in addition to the relative abundance and strain-level heterogeneity of *Cutibacterium acnes*, alongside functional shifts in the cutaneous microbiota. These changes activate inflammatory pathways that drive lesion formation and clinical heterogeneity. Molecular studies identified key virulence factors including lipases, porphyrins, and biofilm formation that interact with host immunity to sustain inflammation. Diagnosis remains primarily morphological, with severity grading guiding therapy. Management targets multiple pathogenic pathways using combination regimens that include topical retinoids, benzoyl peroxide, antimicrobials, hormonal therapies, and systemic agents. Oral isotretinoin remains the most effective treatment for severe acne due to its pleiotropic effects, although it requires careful monitoring because of adverse effects and teratogenicity. Increasing antimicrobial resistance highlights the importance of antibiotic stewardship. Emerging management and prevention strategies include microbiome-modulating approaches (e.g., bacteriophages and targeted peptides), vaccines against *C. acnes* virulence factors, and artificial intelligence–assisted diagnostic tools. The substantial psychosocial burden, including anxiety and depression, is increasingly recognized.

Conclusions: Acne vulgaris is best conceptualized as a complex disorder of the pilosebaceous

unit that reflects the convergence of dermatologic, microbiologic, endocrine, immunologic, and psychosocial processes. Advances in microbiome research, immunology, and sebaceous gland biology are redefining the conceptual framework of acne pathogenesis and may enable future therapies that specifically modulate microbial and inflammatory pathways. Such innovations hold promise for transformative strategies for acne vulgaris prevention and management.

Keywords: Acne Vulgaris; *Cutibacterium acnes*; Skin Microbiome; Pilosebaceous Unit; Acne Pathogenesis; Acne Diagnosis; Acne Management; Dermatologic Inflammation

Abbreviations

AAD: The American Academy of Dermatology; AI: Artificial intelligence; BAD: The British Association of Dermatologists; CAMP: Christie-Atkins-Munch-Petersen factors; DALY: Disability-Adjusted Life-Year; EADV: The European Academy of Dermatology and Venereology; FoxO1: Forkhead box protein O1; GAGS: The Global Acne Grading System; GBD: The Global Burden of Disease study; HRQoL: Health-Related Quality of Life; IGA: The Investigator Global Assessment; IGF-1: Insulin-like Growth Factor-1; QoL: Quality of Life; SANRA: Scale for the Assessment of Narrative Review Articles; SDI: Sociodemographic Index; Th1: T-helper type 1; Th17: T-helper type 17; TLRs: Toll-Like Receptors

Introduction

Acne vulgaris is a uniquely complex dermatologic disorder that lies at the intersection of microbiology, endocrinology, immunology, and psychosocial medicine [1-3]. This non-life-threatening skin condition persisted and has long been described across cultures and historical periods as presented by Mahmood & Shipman [4], making it one of the most common human disorders [2]. Analyses from the Global Burden of Disease (GBD) study indicated that acne vulgaris remains a leading cause of non-fatal disease burden among adolescents and young adults, with increasing Disability-Adjusted Life-Year (DALY) rankings in individuals aged 10-24 years [5]. An earlier review by Tan & Bhate similarly identified acne vulgaris as the eighth most prevalent human disease globally [1]. An analysis from the GBD Study 2019 by Chen et al. estimated approximately 117 million incident cases and more than 231 million prevalent cases of acne vulgaris worldwide, corresponding to about 5 million DALYs and representing an increase of nearly 48% since 1990 [6]. In addition, the GBD study by Chen et al. showed a higher overall prevalence of acne vulgaris among women and in high-income regions over the past three decades [6]. Despite its ubiquity and clinical familiarity, the exact pathogenesis of acne vulgaris remains incompletely understood [7, 8].

At the center of the contemporary understanding of acne vulgaris lies *Cutibacterium acnes*, which is a lipophilic aerotolerant anaerobic Gram-positive bacterium that typically colonizes the human skin [9-11]. For decades, *C. acnes* was regarded primarily as the pathogenic driver of acne vulgaris [12-14]. The contemporary microbiologic and genomic studies provided in-depth insights *C. acnes* as follows. The bacterium is now recognized as a commensal inhabitant of the pilosebaceous unit, integrated within the complex network of the skin microbiota [15-17]. Within the healthy skin, *C. acnes* participate in a dynamic equilibrium with host epithelial cells and other microbial flora [18, 19]. Increasing evidence indicated that acne vulgaris reflects microbial dysbiosis within the pilosebaceous unit rather than a simple infection by *C. acnes* [20, 21]. This dysbiosis appears to involve shifts in bacterial strain composition, alterations in sebum lipid profiles, and dysregulated host immune responses within the follicular microenvironment [22-24].

Despite decades of research on acne vulgaris pathogenesis and an expanding therapeutic options - from topical retinoids and antimicrobial agents to systemic isotretinoin—the disease continues to impose a substantial burden on the Quality of Life (QoL) and psychological well-being of the affected individuals, as highlighted in a recent systematic review by Layton et al., [25]. The disease most commonly emerges during adolescence, a developmental stage in which the physical appearance carries a high social and psychological significance [26, 27]. Consequently, the psychological burden of acne vulgaris may approach that associated with many chronic systemic disorders as highlighted by several studies [28-31]. Specifically, Cresce et al., showed that acne vulgaris can impair Health-Related Quality of Life (HRQoL) to a degree comparable to that observed in several major medical conditions including asthma, epilepsy, diabetes mellitus, back pain, arthritis, and coronary heart disease [31]. Their findings highlighted that acne vulgaris and related inflammatory dermatoses such as rosacea should not be regarded as trivial cosmetic concerns but rather as conditions capable of producing substantial psychosocial morbidity [31].

This significant clinical and psychosocial burden of acne vulgaris, together with its complex and incompletely understood pathogenesis, highlights the continuous need for a deeper understanding of the disease. Over the past two decades, advances in microbial genomics, skin microbiome research, and molecular immunology have reshaped the prevailing concepts of acne vulgaris pathogenesis, revealing intricate interactions among microbial ecology, follicular keratinization, sebaceous gland activity, and host inflammatory responses within the pilosebaceous unit. At the same time, important questions remain regarding the mechanisms that initiate follicular dysbiosis, the determinants of disease severity, and the strategies required for sustained disease management. In this context, the current review aimed to synthesizes current knowledge on the microbiology of *Cutibacterium acnes*, the epidemiology and pathogenesis of acne vulgaris, diagnostic principles, and contemporary management strategies, while also addressing the substantial psychosocial burden of disease and the unresolved scientific questions about this widely prevalent dermatologic condition.

Methods

This narrative review was guided by the principles outlined in the Scale for the Assessment of Narrative Review Articles (SANRA) tool [32, 33]. A structured literature search was performed in PubMed/MEDLINE to identify the relevant publications addressing the microbiology of *C. acnes* and the epidemiology, pathogenesis, diagnosis, management, prevention, and psychosocial aspects of acne vulgaris. PubMed/MEDLINE was selected as the sole source because it is the leading biomedical database and offers a broad coverage of the clinically relevant literature across dermatology and related biomedical disciplines, thereby providing an appropriate

Table 1: Description of the spectrum of lesions encountered in acne vulgaris.

Lesion type	Pathologic mechanism	Clinical appearance	Inflammatory status
Microcomedone	Keratinocyte retention	Microscopic	Non-inflammatory
Closed comedones	Occluded follicle	Whitehead	Non-inflammatory
Open comedones	Dilated follicle	Blackhead	Non-inflammatory
Papule	Dermal inflammation	Erythematous bump	Inflammatory
Pustule	Neutrophilic inflammation	Pus-filled lesion	Inflammatory
Nodule	Deep dermal inflammation	Large painful lesion	Inflammatory
Cyst	Severe inflammation	Fluctuant lesion	Inflammatory

foundation for a focused narrative review on *Cutibacterium acnes* and acne vulgaris. Articles published up to 1 March 2026 were considered. The search strategy used combinations of the following keywords: *Cutibacterium acnes*, *Propionibacterium acnes*, acne vulgaris, acne pathogenesis, skin microbiome, acne treatment, and acne epidemiology.

Titles and abstracts were screened by the first and senior authors, and relevant full-text articles were evaluated for inclusion according to their relevance to the objectives of the review. Priority was given to clinical studies, microbiologic investigations, major dermatology reviews, and guideline statements issued by recognized dermatologic societies, including the American Academy of Dermatology (AAD), the British Association of Dermatologists (BAD), and the European Academy of Dermatology and Venereology (EADV). Because the present work was designed as a narrative review rather than a systematic review or meta-analysis, formal quantitative synthesis and risk-of-bias assessment were not performed. Instead, the available evidence was critically appraised and synthesized to provide a comprehensive overview of current knowledge while avoiding overinterpretation of preliminary findings.

Definition, Nomenclature, and Grading of Acne Vulgaris

Acne vulgaris can be defined as a multi-factorial chronic inflammatory disorder of the pilosebaceous unit which is a complex anatomical structure composed of the hair follicle, sebaceous gland, follicular ductal epithelium, and the associated arrector pili muscle [34-36]. Clinically, the disease is characterized by a spectrum of lesions that include microcomedones, comedones, inflammatory papules, pustules, nodules, and, in more severe cases, cystic lesions and permanent scarring as presented in (Table 1) [37, 38]. Acne vulgaris preferentially affects sebaceous gland-rich regions of the skin, particularly the face, upper chest, shoulders, and back, where the density and activity of sebaceous follicles are greatest [38, 39].

Microcomedone is the earliest identifiable lesion in acne vulgaris pathogenesis and it can be described as a microscopic structure formed by abnormal keratinocyte proliferation and impaired desquamation within the follicular infundibulum, accompanied by accumulation of sebum and cellular debris [40]. Progressive enlargement of the microcomedone results in the formation of a clinically visible comedo. These non-inflammatory lesions, collectively termed comedones, are classified into two principal morphologic types [41]. Closed comedones (whiteheads) occur when the follicular orifice remains occluded, whereas open comedones (blackheads) develop when dilation of the follicular opening exposes oxidized keratin and lipid material at the skin surface [42]. Inflammatory lesions, including papules, pustules, nodules, and cystic lesions, arise when follicular rupture, microbial proliferation, and activation of innate immune responses lead to infiltration of inflammatory cells within the perifollicular dermis [43].

From a dermatologic perspective, acne vulgaris lesions represent sequential stages in the evolution of follicular pathology. Early comedonal lesions reflect abnormal follicular keratinization and sebum retention, whereas inflammatory lesions develop when disruption of the follicular wall permits extrusion of keratin, sebum, and microbial antigens into the surrounding dermis, triggering an inflammatory cascade [44]. Thus, acne vulgaris can be regarded as the clinical manifestation of multiple interacting disturbances within the pilosebaceous unit, involving alterations in follicular keratinization, sebaceous gland activity, microbial ecology, and host inflammatory responses [45, 46].

In clinical dermatology, accurate assessment of acne vulgaris severity is essential for guiding therapeutic decisions, monitoring treatment response, and standardizing outcomes in clinical research [47, 48]. Several complementary approaches are used to evaluate disease severity, including global clinical grading, lesion-counting methods, and image-based assessment techniques [48]. Global grading systems rely on an overall clinical evaluation of lesion morphology and distribution, whereas lesion-counting methods quantify comedonal and inflammatory lesions to generate numerical severity scores [49]. Over time, a number of grading instruments have been proposed, including the Cook photographic scale [50], the Leeds acne grading system [51], the Global Acne Grading System (GAGS) [52], and simplified global assessments such as the Investigator Global Assessment (IGA) by the U.S. Food and Drug Administration [48]. A brief overview of these grading systems is highlighted in (Table 2).

Although widely used, these systems differ in methodology and may show variability between observers, and many do not fully depict features such as scarring, erythema, or post-inflammatory pigmentary changes [48]. Consequently, efforts are ongoing to develop more objective and reproducible approaches to acne assessment, including digital imaging and Artificial Intelligence (AI)-assisted analysis [53, 54].

Epidemiology of Ance Vulgaris

Acne vulgaris is considered among the most common disorders of the skin and remains a major contributor to dermatologic morbidity worldwide [55]. The condition arises predominantly during adolescence and early adulthood, reflecting the profound influence of pubertal hormonal changes on sebaceous gland activity and follicular physiology [38]. Numerous epidemiologic studies sought to quantify the prevalence of acne vulgaris, and the widely cited estimates suggest that a substantial proportion of adolescents experience the disorder

during this developmental period [2, 56-58]. However, accurate estimates of lifetime prevalence of acne vulgaris remain difficult to establish. Variations in study designs, diagnostic criteria, and case definitions, together with reliance on self-reported disease in many population-based surveys, contribute to considerable uncertainty in prevalence estimates of the disease. Moreover, the inherently fluctuating clinical course of acne vulgaris which is characterized by cycles of remission and exacerbation further complicates efforts to define its true lifetime prevalence.

Recent analyses from the GBD Study 2021 highlighted the substantial and increasing burden of acne vulgaris among adolescents and young adults worldwide [56]. Between 1990 and 2021, the global age-standardized prevalence rate of acne among individuals aged 10-24 years increased from approximately 8,563 to 9,790 cases per 100,000 population, corresponding to a modest but consistent annual rise of about 0.4% [56]. Age-standardized incidence and DALY rates showed similar rising trends during this period [56]. Substantial geographic variation was also observed, with the region of Western Europe reporting the highest prevalence, incidence, and DALY rates of acne, whereas the North Africa and Middle East region demonstrated the most pronounced increases over time [56]. Across socio-demographic strata, countries with a high Sociodemographic Index (SDI) bear the greatest overall burden of acne vulgaris, although the prevalence has increased most rapidly in lower-middle SDI regions [56]. In 2021, the age-standardized prevalence among young women was approximately 25% higher than among young men. Prevalence peaked in adolescents aged 15-19 years, whereas the most pronounced increases since 1990 have occurred among those aged 10-14 years. These patterns highlighted the substantial regional and demographic variability in the global burden of acne vulgaris [56].

The onset of acne vulgaris typically coincides with puberty, when rising androgen levels stimulate enlargement of the sebaceous glands and increased sebum production [59]. Disease prevalence peaks during mid- to late adolescence, particularly between 15 and 18 years of age, although acne frequently persists beyond adolescence and may extend into adulthood [60]. In recent decades, increasing attention has been directed toward adult-onset and persistent acne, particularly among women [60-62]. In some populations, up to one third of adult women report active acne lesions, which highlights the growing recognition of acne as a disorder that may extend well beyond adolescence [63, 64].

Before puberty, acne vulgaris is not uniformly distributed between boys and girls. In a population-based cohort of children aged 7-12 years, the annual age- and sex-adjusted incidence of acne was substantially higher in girls than in boys (89.2 *vs*. 28.2 per 10,000 person-years), with incidence increasing progressively across the pre-adolescent years [65]. During later adolescence, however, males often develop more severe inflammatory disease, including nodular and truncal involvement [2, 60]. In adulthood, the distribution again shifts, with persistent or late-onset acne occurring more frequently in women, typically involving the lower face and jawline and, in some cases, associated with menstrual cyclicity or endocrine disorders such as polycystic ovary syndrome [66-69].

Although acne vulgaris occurs worldwide, epidemiologic patterns suggest that environmental and lifestyle factors may influence disease expression [1, 2, 70]. Historically, populations consuming traditional diets characterized by a low glycemic load have been reported to exhibit relatively low acne prevalence as reviewed by Meixiong et al., [71]. For example, among the Kitavan Islanders of Papua New Guinea and the Ache hunter-gatherers of Paraguay, no cases of acne were observed across adolescent and adult age groups, findings attributed to traditional diets low in refined carbohydrates [72]. In contrast, increasing urbanization and the adoption of Western dietary patterns - particularly those characterized by high intake of refined carbohydrates characterized by high glycemic load, processed sugars, and insulinotropic dairy intake have been associated with higher rates of acne vulgaris [73-75]. These dietary exposures have been shown to increase circulating insulin and Insulin-like Growth Factor-1 (IGF-1) levels, thereby activating the PI3K-Akt-mTORC1 pathway, which promotes sebaceous lipogenesis and follicular hyperkeratinization [76]. While the evidence linking diet directly to acne pathogenesis remains incomplete, these observations raise the possibility that metabolic and endocrine pathways influenced by dietary factors may contribute to variations in disease severity [77-79].

Beyond age and dietary factors, family history is a strong predictor of susceptibility to acne vulgaris [80, 81]. Evidence from twin studies and genome-wide association analyses indicates that genetic variation influences multiple biologic pathways involved in acne pathogenesis, including sebaceous gland activity, androgen metabolism, inflammatory signaling, and follicular keratinization [81, 82]. Although the exact genetic architecture of acne remains incompletely defined, available data suggest that susceptibility is polygenic and multifactorial as presented by Teder-Laving et al., [83]. This reflects the interaction of numerous genetic variants with hormonal and environmental influences [84].

Etiology of Acne Vulgaris

The etiology of acne vulgaris has traditionally been conceptualized as the result of four interrelated pathogenic processes: increased sebum production, abnormal follicular keratinization, colonization of the pilosebaceous unit by *C. acnes*, and activation of inflammatory immune responses [44]. This framework has long provided a useful foundation for understanding disease development. Increasing evidence, however, indicates that these processes do not occur in isolation but rather within a broader ecological and immunologic network involving dynamic interactions among sebaceous gland physiology, follicular epithelial biology, the cutaneous microbiome, and host immune signaling pathways [21].

The Pilosebaceous Unit as an Immuno-metabolic Niche in Acne Vulgaris

The pilosebaceous unit functions as a highly specialized microenvironment that supports a diverse community of microorganisms [85]. Rather than being sterile, this niche harbors a complex cutaneous microbiota that include *C. acnes*, *Staphylococcus epidermidis*, *Malassezia* species, and a range of aerobic and anaerobic bacteria [86, 87]. These organisms interact dynamically with each other and with host epithelial and immune cells [88, 89]. Under physiologic conditions, this system exists in a state of relative ecological equilibrium [85]. However, in acne vulgaris, the alterations in sebum composition, follicular architecture, or host immune signaling may disrupt this balance, promoting microbial dysbiosis and the emergence of inflammatory disease [20, 90].

Central to the acne vulgaris etiology is *C. acnes*, a lipophilic, anaerobic Gram-positive bacterium uniquely adapted to the lipid-rich environment of sebaceous follicles [91]. The organism metabolizes

sebum triglycerides through the action of bacterial lipases, generating free fatty acids that can contribute to local inflammation [92, 93]. Notably, *C. acnes* is abundant in both healthy and acne-affected skin, a finding that historically complicated efforts to define its pathogenic role [93, 94]. Advances in genomic sequencing have helped clarify this apparent paradox [24]. Multiple phylogenetic lineages of *C. acnes* have been identified, and these strains differ in their metabolic properties, virulence determinants, and ability to stimulate host inflammatory responses [95-97]. Certain lineages are enriched within acne vulgaris lesions, whereas others predominate in healthy skin [98]. These observations suggest that acne may arise not simply from the presence of *C. acnes*, but from strain-level shifts within the follicular microbiome that alter host-microbial interactions within the pilosebaceous unit [99, 100].

Pathogenesis of Acne Vulgaris

The development of acne vulgaris lesions proceeds through a series of biologically interconnected events within the pilosebaceous unit [101]. Central to this process is the sebaceous gland, whose activity is strongly influenced by androgenic stimulation during puberty [102]. Under androgen signaling, sebocytes produce sebum - a complex lipid mixture composed primarily of triglycerides, wax esters, squalene, and cholesterol esters [103]. Increased sebum production contributes to acne pathogenesis through several mechanisms [104]. Excess sebum provides a lipid-rich substrate that supports microbial growth within the follicular canal, alters the physicochemical environment of the follicle, and influences keratinocyte differentiation within the follicular infundibulum [103, 105]. In addition, oxidative modification of sebum lipids, particularly squalene, can generate bioactive lipid mediators that promote local inflammation and contribute to the initiation of acne lesions [103, 106].

It is worth emphasizing that androgen excess alone does not fully account for the initiation and persistence of acne vulgaris. Increasing evidence supports a central role for the IGF-1 signaling axis as a key upstream regulator of sebaceous gland activity and follicular keratinization [107-109]. During puberty, rising IGF-1 levels - driven by growth hormone secretion and modulated by nutritional factors - activate the PI3K-Akt-mTORC1 pathway, promoting sebocyte proliferation, lipogenesis, and keratinocyte growth [108]. In parallel, IGF-1 enhances androgen receptor signaling and suppresses the activity of forkhead box protein O1 (FoxO1), a transcriptional inhibitor of sebaceous gland function, thereby amplifying androgenic effects at the cellular level [110, 111]. This integrated endocrine-metabolic signaling framework provides a more comprehensive explanation for acne pathogenesis, particularly in cases where circulating androgen levels are within normal ranges [112]. It also offers a biologically plausible link between acne and dietary patterns characterized by high glycemic load and insulinotropic dairy intake, both of which have been shown to increase IGF-1 activity and may contribute to disease persistence into adulthood.

The earliest structural event in acne pathogenesis is abnormal differentiation of keratinocytes within the follicular infundibulum [113]. Instead of undergoing orderly desquamation, follicular keratinocytes accumulate within the follicular canal, leading to the formation of a keratinous plug [44]. This microscopic lesion, known as the microcomedone, represents the fundamental precursor from which all clinically recognizable acne lesions develop [40, 114]. Several molecular mechanisms have been implicated in this process, including dysregulation of keratinocyte proliferation, alterations in retinoid signaling pathways, and activation of proinflammatory cytokines within the follicular microenvironment [115].

Within the obstructed follicle, sebum accumulation and reduced oxygen tension create conditions favorable for the growth of anaerobic bacteria such as *C. acnes* [38, 93]. The organism proliferates and produces various metabolites and virulence factors that influence host tissues. These include lipases that hydrolyze sebum triglycerides, proteases that degrade extracellular matrix, porphyrins capable of generating reactive oxygen species [93]. Through these mechanisms, bacterial activity contributes to local inflammation [116]. Evidence increasingly indicates that inflammatory signaling may precede the appearance of clinically visible lesions [117]. Keratinocytes and resident immune cells within the follicular unit express pattern-recognition receptors, including Toll-Like Receptor 2 (TLR-2), which recognize microbial components derived from *C. acnes* [118, 119]. Activation of these receptors stimulates the production of proinflammatory cytokines, including interleukin-1β, interleukin-8, and tumor necrosis factor-α, which promote recruitment of neutrophils and other inflammatory cells into the perifollicular dermis [120, 121]. This inflammatory cascade contributes to the transformation of the microcomedone into clinically apparent inflammatory lesions, such as papules and pustules [122]. Taken together, current evidence supports a model in which acne develops through complex interactions among endocrine stimulation, microbial dynamics, follicular structural changes, and host immune responses. Rather than reflecting a single pathogenic trigger, acne is best understood as the consequence of disrupted homeostasis within the pilosebaceous ecosystem [123].

Molecular Microbiology of *Cutibacterium acnes*

The bacterium now designated *Cutibacterium acnes* was historically classified as *Propionibacterium acnes* until a taxonomic revision of the genus in 2016 reassigned the organism, reflecting its distinctive phylogenetic position among anaerobic Gram-positive commensals of human skin [124]. A slow-growing, aerotolerant anaerobic bacillus, *C. acnes* preferentially inhabit sebaceous follicles, where lipid substrates are plentiful [93, 125]. The organism is highly adapted to the specialized microenvironment of the pilosebaceous unit [15]. Genomic studies have identified a broad repertoire of determinants involved in lipid utilization, biofilm formation, and interactions with host immune pathways, features that likely facilitate the persistence of *C. acnes* within the follicular niche and contribute to its complex role in acne pathobiology [126, 127]. Supporting this concept, genome-wide analyses by Podbielski et al., identified consistent genetic differences between colonizing and disease-associated *C. acnes* strains, primarily involving metabolic and DNA repair genes suggesting that pathogenic behavior may reflect metabolic adaptation to the follicular environment [128].

Whole-genome sequencing has revealed that *C. acnes* comprise several phylogenetic lineages, generally classified into phylotypes IA1, IA2, IB, IC, II, and III as shown in (Table 3) [96, 129-132].

Importantly, epidemiologic studies of the skin microbiome demonstrate that specific phylotypes are enriched in acne lesions, while others are associated with healthy skin [22, 133]. Strains belonging to the IA1 lineage appear particularly associated with inflammatory acne [22, 127, 134]. These strains possess genomic

elements encoding virulence factors that enhance inflammatory potential [127]. Conversely, type II strains are frequently isolated from healthy follicles and may even exert protective effects by competing with pathogenic strains [134, 135]. These observations suggest that acne may represent a shift in *C. acnes* strain ecology rather than simple bacterial overgrowth. In other words, disease may arise when inflammatory strains dominate the microbial community within the follicle [89].

Virulence Factors and Bacterial Physiology

Although *C. acnes* is a common commensal inhabitant of human skin, several bacterial products can promote inflammation within the follicular microenvironment [93, 136, 137]. Among the most important are bacterial lipases, which hydrolyze sebum triglycerides into free fatty acids [138, 139]. These lipid metabolites possess proinflammatory properties and may contribute to damage of follicular epithelial cells [10]. In addition, free fatty acids can alter the local *pH* and permeability of the follicular wall, thereby facilitate inflammatory cell infiltration and amplify the inflammatory response [93, 140]. *C. acnes* produce porphyrins, including coproporphyrin III, which act as photosensitizers and can generate reactive oxygen species in the presence of light and oxygen within the follicular microenvironment [141, 142]. The resulting oxidative stress may promote local tissue injury and activate inflammatory signaling pathways within the pilosebaceous unit [143].

Another group of *C. acnes* virulence-associated molecules are the Christie-Atkins-Munch-Petersen (CAMP) factors, a family of pore-forming proteins capable of disrupting host cell membranes [143, 144]. Experimental studies have shown that CAMP proteins can activate inflammatory signaling pathways in keratinocytes and macrophages, further contributing to the inflammatory cascade observed in acne lesions [145, 146]. In addition to these secreted factors, *C. acnes* is capable of forming biofilms within the follicular canal [147, 148]. Biofilms consist of structured bacterial communities embedded within an extracellular polymeric matrix that enhances bacterial survival by protecting organisms from host immune defences and antimicrobial agents [149]. The presence of biofilms within sebaceous follicles may therefore contribute to the persistence of *C. acnes* in acne lesions and may partly explain the incomplete response to antimicrobial therapy observed in some patients [149].

Host Immune Responses

The inflammatory component of acne vulgaris reflects activation of both innate and adaptive immune pathways within the pilosebaceous unit [121]. Early inflammatory signaling is largely mediated by innate immune mechanisms [150]. Keratinocytes and sebocytes express pattern-recognition receptors, including TLRs, which recognize microbial molecules such as lipoteichoic acid and peptidoglycan derived from *C. acnes* [123]. Among these receptors, TLR-2 appears to play a central role in acne-associated inflammation [120]. Activation of TLR-2 by bacterial components initiates intracellular signalling cascades that result in the production of proinflammatory cytokines, including IL-1β, IL-6, TNF-α, and IL-8 [119, 120]. These mediators promote the recruitment of neutrophils and macrophages to the follicular unit [123]. Activated neutrophils release proteolytic enzymes and reactive oxygen species, which contribute to follicular wall disruption and dermal inflammation, ultimately giving rise to the papules and pustules characteristic of inflammatory acne lesions [44, 151].

Adaptive immune responses also contribute to the inflammatory milieu of acne [123]. T lymphocytes infiltrate developing lesions and produce cytokines consistent with T-helper type 1 (Th1) and T-helper type 17 (Th17) immune responses [151]. In particular, Th17-mediated signalling has been implicated in sustaining chronic inflammation within acne lesions [152]. IL-17 promotes neutrophil recruitment and amplifies local inflammatory cascades within the follicular microenvironment [153]. Although both innate and adaptive immune pathways are clearly involved in acne pathogenesis, the exact interplay between these systems and their relative contributions to disease initiation and progression remain areas of ongoing investigation [123].

Clinical Diagnosis of Acne Vulgaris

The diagnosis of acne vulgaris is primarily clinical and relies on careful assessment of lesion morphology, distribution, and disease chronology [38]. Dermatologic examination typically reveals a mixture of comedonal and inflammatory lesions arising within sebaceous gland-rich regions of the skin [38]. The face is most frequently affected, particularly the forehead, cheeks, and chin, although involvement of the upper chest, shoulders, and back is also common [38]. The presence of comedones - either open (blackheads) or closed (whiteheads) - is the defining diagnostic feature of acne, reflecting obstruction of the follicular infundibulum and distinguishing acne from many other follicular inflammatory disorders [38, 44].

Clinical severity is generally classified along a spectrum to guide therapeutic decision-making [154-156]. Mild acne is characterized predominantly by comedonal lesions with only occasional inflammatory papules. Moderate acne presents with a greater number of inflammatory papules and pustules and may include limited nodular lesions. Severe acne is marked by extensive inflammatory disease with numerous papules, pustules, and nodules, often associated with an increased risk of scarring [48]. At the most severe end of the spectrum, nodulocystic acne consists of deep inflammatory nodules and cysts that frequently lead to permanent scarring and therefore require prompt and aggressive management [157, 158]. Accurate assessment of acne vulgaris severity is essential for selecting appropriate therapy, monitoring treatment response, and preventing long-term complications such as scarring and post-inflammatory pigmentary change [159, 160].

Although the diagnosis is usually straightforward, several dermatologic conditions can mimic acne vulgaris and should be considered during clinical evaluation [38]. These include rosacea, gram-negative folliculitis, perioral dermatitis, drug-induced acneiform eruptions, and *Malassezia* folliculitis [38, 161]. A key diagnostic clue lies in the presence or absence of comedones; their presence strongly supports the diagnosis of acne vulgaris, whereas their absence should prompt consideration of alternative follicular or inflammatory dermatoses [38, 161, 162]. Additional clinical features—such as the distribution of lesions, the presence of erythema or flushing, medication history, and associated systemic findings - may further aid in distinguishing these conditions [162]. From a dermatologic perspective, establishing the correct diagnosis is critically important because management strategies differ substantially among acne and its mimickers [162]. Misdiagnosis may lead to inappropriate use of antibiotics, corticosteroids, or retinoids and may delay effective treatment, thereby increasing the risk of permanent scarring and psychosocial morbidity [163]. Careful clinical evaluation therefore remains the cornerstone of accurate diagnosis and appropriate

management of acne vulgaris.

Management and Prevention of Acne Vulgaris

The management of acne vulgaris is directed toward the principal biologic processes underlying disease pathogenesis: sebaceous gland hyperactivity, abnormal follicular keratinization, microbial proliferation within the pilosebaceous unit, and inflammatory immune signalling [117, 154, 164, 165]. Contemporary therapeutic strategies therefore aim to modulate several of these mechanisms simultaneously, and combination therapy has been the standard approach in clinical practice [117, 166]. Current acne treatment recommendations emphasize early intervention, appropriate severity-based escalation of therapy, and careful stewardship of antimicrobial agents to minimize the development of bacterial resistance [167, 168].

Topical agents constitute the foundation of acne management and are generally recommended as first-line therapy for mild disease and as adjunctive treatment for more severe forms [168]. Topical retinoids remain the cornerstone of acne therapy because they directly target the earliest event in acne pathogenesis; the formation of the microcomedone [169]. Agents such as tretinoin, adapalene, and tazarotene normalize follicular keratinization, promote desquamation of keratinocytes within the follicular infundibulum, and prevent the formation of new comedonal lesions [170]. In addition to their comedolytic activity, retinoids exert anti-inflammatory effects, including modulation of toll-like receptor signalling and cytokine production [171].

Additionally, benzoyl peroxide is used which is a potent bactericidal agent that generates reactive oxygen species capable of rapidly killing *C. acnes* [172]. Unlike antibiotic therapies, benzoyl peroxide does not promote bacterial resistance and is therefore a key component of modern acne treatment regimens [173]. For this reason, clinical guidelines recommend that topical antibiotics be combined with benzoyl peroxide whenever possible to reduce the emergence of resistant bacterial strains [174].

Topical antibiotics, most commonly clindamycin or erythromycin, reduce bacterial colonization and exert anti-inflammatory effects within the follicle [175]. However, widespread use of topical antibiotics has contributed to increasing rates of antimicrobial resistance among *C. acnes* strains [176, 177]. Clinical guidelines therefore discourage antibiotic monotherapy and recommend combination therapy with benzoyl peroxide or topical retinoids to preserve antimicrobial effectiveness [154, 156].

Systemic antibiotics are frequently prescribed for moderate to severe inflammatory acne [154]. The tetracycline class - including doxycycline, minocycline, and the narrow-spectrum tetracycline sarecycline - remains the most commonly used group [178, 179]. These agents exert both antibacterial and anti-inflammatory effects, including suppression of neutrophil chemotaxis and inhibition of proinflammatory cytokine production [180]. Nevertheless, concerns regarding antibiotic resistance have prompted guidelines recommending that systemic antibiotics be used for limited durations and in conjunction with topical therapies rather than as long-term monotherapy [181].

Hormonal therapy represents an important treatment option in female patients, particularly those with adult-onset or hormonally mediated acne [182, 183]. Combined oral contraceptives reduce ovarian androgen production and increase sex hormone-binding globulin levels, thereby decreasing free androgen activity and sebaceous gland stimulation [184, 185]. Spironolactone, an androgen receptor antagonist, is widely used in adult female acne and may be particularly beneficial in patients with clinical features of hyperandrogenism or endocrine disorders such as polycystic ovary syndrome [186, 187].

Among currently available therapies, oral isotretinoin remains the most transformative treatment for severe acne [154, 159, 188]. Isotretinoin uniquely targets multiple pathogenic mechanisms simultaneously, including profound suppression of sebaceous gland activity, normalization of follicular keratinization, reduction of *C. acnes* colonization, and attenuation of inflammatory signalling [108]. As a result, a single treatment course can induce prolonged remission and, in some patients, complete resolution of disease [189]. Despite its remarkable efficacy, isotretinoin is associated with important adverse effects. Common reactions include mucocutaneous dryness, cheilitis, and laboratory abnormalities involving serum lipids or liver enzymes [190, 191]. More importantly, isotretinoin is highly teratogenic, necessitating strict pregnancy-prevention measures and careful patient counselling [192]. Current monitoring strategies generally include baseline evaluation of lipid levels and liver function, followed by repeat testing during therapy, particularly at peak dosage or in patients with additional risk factors [193].

The widespread use of antibiotics in acne treatment has contributed to the emergence of antibiotic-resistant *C. acnes* strains, particularly with macrolide antibiotics such as erythromycin and clindamycin [181, 194]. Resistance mechanisms include mutations affecting ribosomal binding sites and acquisition of resistance genes [195]. These trends have highlighted the importance of antibiotic stewardship in dermatology, prompting recommendations to restrict antibiotic use, limit treatment duration, and preferentially employ non-antibiotic therapies when appropriate [196, 197].

Primary prevention of acne remains challenging because hormonal influences and genetic susceptibility play dominant roles in disease initiation [198]. Nevertheless, several strategies may mitigate disease severity. Early treatment of comedonal lesions may reduce progression to inflammatory acne and prevent scarring [17]. Additional preventive measures include avoidance of comedogenic cosmetic products, gentle cleansing and skin-care practices, and discouraging mechanical manipulation of lesions [199, 200]. Emerging research suggests that modulation of the cutaneous microbiome may represent a future strategy for acne prevention and treatment [201]. Investigational approaches include probiotics, bacteriophage therapy, and targeted antimicrobial peptides designed to selectively suppress pathogenic *C. acnes* strains while preserving commensal microbial communities [202, 203]. Another promising avenue involves the development of acne vaccines targeting secreted virulence factors of *C. acnes* [204, 205]. Experimental studies have demonstrated that vaccines directed against CAMP factors, pore-forming proteins implicated in inflammatory signalling, can reduce inflammatory responses in preclinical models [206]. Although these approaches remain investigational, they illustrate the potential for immune-based therapies to provide highly specific interventions against acne-associated bacterial mechanisms without disrupting the broader skin microbiome [201, 202].

Emotional and Psychosocial Burden

Although acne vulgaris is rarely life-threatening, its psychological

and social consequences can be substantial [207]. The disease frequently emerges during adolescence and early adulthood, a developmental period in which physical appearance plays a central role in the formation of self-identity and social integration. Consequently, even relatively mild facial disease may produce disproportionate emotional distress [28]. Numerous clinical studies have documented associations between acne and reduced self-esteem, social withdrawal, anxiety symptoms, and depressive disorders [26, 208-212].

The psychosocial burden of acne is not limited to visible skin changes alone. Facial lesions often occur in highly visible areas of the body and may therefore influence interpersonal interactions, educational participation, and occupational opportunities. Several studies using validated HRQoL instruments have demonstrated that the psychological impact of acne may approach that observed in other chronic medical conditions [213-217]. Patients frequently report embarrassment, stigmatization, and fear of negative social judgment [218, 219]. In severe cases, these experiences may lead to avoidance behaviors, impaired QoL, and diminished psychosocial functioning [28, 220].

Importantly, the psychosocial burden of acne vulgaris does not correlate perfectly with clinical severity; even patients with relatively mild disease may experience substantial psychological impairment. Recognition of these effects has important clinical implications. Increasingly, dermatologists consider psychological well-being as an integral component of acne management [221]. Early and effective treatment would reduce the risk of permanent scarring and mitigate the development of long-term psychosocial morbidity [222, 223]. For this reason, many clinicians advocate a proactive therapeutic approach when acne is associated with significant emotional distress, particularly during adolescence when vulnerability to social stigma and negative self-perception may be greatest [28].

Can Acne Be Controlled?

Whether acne vulgaris can ultimately be well-controlled remains uncertain. The disorder arises from the convergence of several fundamental biological processes - including androgen-driven sebaceous gland activity, follicular keratinization, microbial ecology within the pilosebaceous unit, and host inflammatory responses. Because these processes are integral to normal skin physiology, complete eradication of acne is unlikely with current therapeutic modalities. Nevertheless, emerging insights from microbiology, immunology, and sebaceous gland biology raise the possibility that future interventions could fundamentally alter the natural history of the disease [224].

One promising area of investigation involves microbiome engineering [201]. Increasing evidence indicates that acne is associated with shifts in the composition and functional behavior of microbial communities including *Cutibacterium acnes* within sebaceous follicles [21]. Strategies aimed at selectively modulating this microbial ecosystem - including probiotic approaches, bacteriophage therapy, and targeted antimicrobial peptides - may offer the ability to suppress acne-associated bacterial lineages while preserving commensal organisms that contribute to skin homeostasis [225]. Such approaches could represent a paradigm shift away from broad-spectrum antimicrobial therapy toward precision manipulation of the cutaneous microbiome.

A second avenue of research focuses on targeted immunologic modulation. Advances in understanding the inflammatory networks underlying acne have highlighted the importance of innate immune signalling pathways, including interleukin-1–mediated inflammasome activation and Th17 responses [226]. Therapeutic strategies that selectively attenuate these inflammatory pathways - without disrupting normal microbial ecology - may allow for more precise control of acne-associated inflammation. Similar approaches have already transformed the treatment of other inflammatory dermatoses, suggesting that cytokine-directed therapies could eventually play a role in severe or treatment-resistant acne [227].

Finally, progress in sebaceous gland biology may offer new opportunities for disease prevention. The sebaceous gland is central to acne pathogenesis, yet the molecular mechanisms governing sebocyte differentiation, lipid synthesis, and sebaceous gland remodelling remain incompletely understood [101]. Advances in lipidomics, endocrine signalling, and stem cell biology may ultimately enable the development of therapies capable of modulating sebum production with greater specificity and fewer systemic effects than current retinoid-based treatments [228]. Although the full control of acne vulgaris may remain elusive, continued advances in microbiome science, immunology, and sebaceous gland physiology are reshaping the conceptual framework of the disease [21, 89, 229]. These developments suggest that future therapies may move beyond symptomatic control toward specific biologic modulation of the pilosebaceous ecosystem, with the potential to dramatically reduce the global burden of acne.

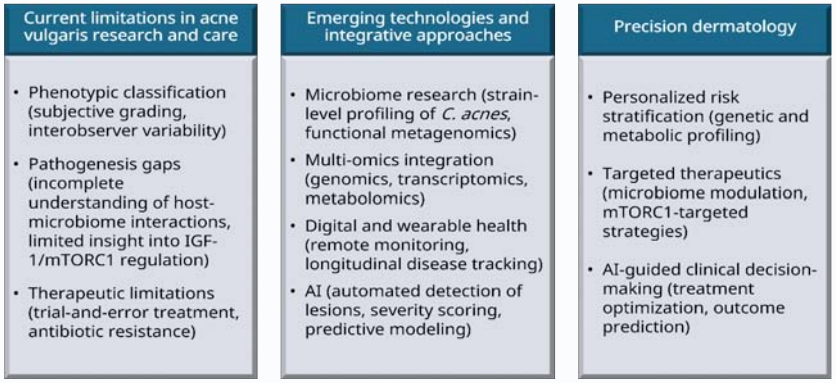

Figure 1: The transition from current limitations in acne research and clinical care to emerging technologies and future precision dermatology approaches. IGF-1: Insulin-like Growth Factor-1, mTORC1: mechanistic Target Of Rapamycin Complex 1, AI: Artificial Intelligence, *C. acnes*: *Cutibacterium acnes*.

Table 2: Commonly used global acne vulgaris grading systems.

Acne Grading system	Methodological basis	Strengths	Limitations
Pillsbury scale	Qualitative clinical classification based on predominant lesion morphology and distribution (Grades I-IV)	Historically foundational; easy to apply in routine clinical settings; captures broad disease severity patterns	Poor granularity and sensitivity to change; high subjectivity; limited reproducibility; not suitable for clinical trials or longitudinal outcome assessment
Cook photographic scale	Standardized comparison with reference photographic panels representing increasing acne severity	Provides visual standardization; improves interobserver consistency compared with purely clinical judgment; useful in multicenter settings	Time-intensive; dependent on image quality and lighting standardization; limited adaptability to diverse skin phototypes; may not capture subtle changes in lesion counts
Leeds grading system	Quantitative lesion counting combined with photographic standards (Leeds technique and revised Leeds scale)	Objective and reproducible; sensitive to incremental changes; widely validated in clinical research settings	Requires training and calibration; time-consuming in busy clinics; lesion counting may be impractical in severe or truncal acne; interobserver variability persists without standardization
Global Acne Grading System (GAGS)	Composite score based on lesion type (comedones, papules, pustules, nodules) weighted by anatomical region factors	Semi-quantitative and rapid; incorporates anatomical distribution; widely used in both clinical practice and research; better reflects overall disease burden than lesion counts alone	Weighting factors are empirically derived rather than biologically validated; interobserver variability; limited sensitivity to subtle therapeutic changes; underrepresents post-inflammatory sequelae
Investigator Global Assessment (IGA)	Ordinal scale (typically 0-4 or 0-5) based on overall severity using defined descriptors of lesion type and count thresholds	Regulatory acceptance (e.g., the U.S. Food and Drug Administration endpoints); simple and efficient; facilitates standardized outcome reporting in clinical trials	Coarse scale with limited discrimination; ceiling and floor effects; does not adequately capture regional variation or lesion heterogeneity; moderate interobserver variability

Table 3: Phylogenetic classification of *Cutibacterium acnes* and associated virulence and clinical phenotypes.

Phylotype	Phylogenetic classification	Clinical association	Key genomic and functional characteristics	Representative features
IA1	Type IA1 (SLST classes A1–A5; CC18, CC28)	Strongly associated with inflammatory acne lesions	Enriched in virulence-associated genes; increased expression of Christie-Atkins-Munch-Petersen (CAMP) factors, lipases, and porphyrin production; enhanced biofilm formation; promotes Th1/Th17-mediated inflammation	High induction of IL-1β, IL-8; increased porphyrin-mediated oxidative stress; frequent isolation from comedones and pustules
IA2	Type IA2 (SLST classes A6–A10; CC3)	Associated with acne, but less consistently than IA1	Intermediate virulence profile; retains lipase and CAMP factor activity but with lower inflammatory potential; genetically distinct from IA1 despite similar ecological niche	Moderate cytokine induction; found in both lesional and non-lesional skin
IB	Type IB (CC36, CC53)	Mixed association (acne and healthy skin)	Genetically diverse group; variable expression of virulence factors; some strains exhibit biofilm-forming capacity; may act as commensals or opportunistic pathogens depending on host context	Heterogeneous inflammatory response; context-dependent pathogenicity
IC	Type IC (rare lineage)	Rare; limited clinical data	Phylogenetically distinct but poorly characterized; genomic content suggests divergence from IA/IB lineages; functional role remains unclear due to low prevalence	Insufficient data; occasionally detected in skin microbiome studies
II	Type II (CC60, CC72)	Predominantly associated with healthy skin; underrepresented in acne lesions	Lower expression of proinflammatory mediators; reduced porphyrin production; distinct cell surface structures; may contribute to microbiome stability and immune tolerance	Weak induction of inflammatory cytokines; enriched in non-lesional skin
III	Type III (CC77)	Rare; occasionally linked to non-acne conditions (e.g., progressive macular hypomelanosis)	Genetically divergent lineage; unique genomic islands; reduced classical virulence factor expression; distinct metabolic profile	Associated with dyschromia rather than inflammation; low abundance in acne lesions

Future Perspectives

Despite decades of investigation, several fundamental aspects of acne vulgaris remain incompletely understood as shown in (Figure 1). The condition arises within the complex ecological and immunologic environment of the pilosebaceous unit, yet key determinants of disease susceptibility and severity remain elusive. One enduring question concern why only a subset of individuals develop severe inflammatory disease despite near-universal colonization of human skin by *C. acnes* [99]. Contemporary microbiome studies suggest that acne may reflect shifts in microbial community structure and function rather than the presence of a single pathogen, with strain-specific differences and host-microbial interactions playing critical roles in disease expression [202]. As illustrated in Figure 1, current limitations in acne research include reliance on subjective phenotypic classification, incomplete understanding of host-microbiome and IGF-1-mediated pathways, and the continued use of empiric therapeutic strategies.

Emerging technologies may help to better address acne vulgaris as follows. Advances in AI-based dermatologic imaging and analysis are beginning to transform the assessment and grading of acne severity [230, 231]. Machine-learning systems trained on large dermatologic image datasets have demonstrated increasing accuracy in identifying acne lesions, quantifying lesion counts, and classifying disease severity [232]. These tools have the potential to improve diagnostic consistency, facilitate remote monitoring, and enhance clinical research by providing standardized outcome measures for therapeutic trials. In parallel, deeper integration of systems biology approaches - including genomics, microbiome profiling, metabolomics, and immunologic analysis - offers the potential to define disease endotypes and elucidate how microbial ecology, sebaceous gland physiology, and host immune responses converge to produce clinical disease [233, 234]. As summarized in Figure 1, these advances collectively support a transition toward precision dermatology, characterized by individualized risk stratification, targeted therapeutic interventions, and data-driven clinical decision making. Addressing these questions will require close collaboration among dermatologists,

microbiologists, immunologists, bioengineers, and computational scientists, and may ultimately reshape our understanding of acne from a simple bacterial infection to a complex ecosystem disorder of the pilosebaceous unit.

Limitations of the Current Review

This review is subject to limitations inherent to narrative synthesis. The literature search was confined to the PubMed/MEDLINE database and may therefore have omitted relevant studies indexed exclusively in other sources. Moreover, as this work was conducted as a narrative review guided by SANRA rather than as a systematic review or meta-analysis, formalized study selection criteria, risk-of-bias assessment, and quantitative synthesis were not undertaken. Accordingly, the interpretation of evidence remains susceptible to selective reporting and to the heterogeneity of study designs. In addition, the rapidly evolving nature of skin microbiome research and acne immunobiology necessitates caution, as some emerging findings remain preliminary and require validation through larger, methodologically robust mechanistic and clinical investigations.

Conclusions

Acne vulgaris should no longer be regarded as a trivial or purely infectious condition, but rather as a complex disorder of the pilosebaceous unit arising from the convergence of sebaceous biology, follicular keratinization, microbial ecology, and immune dysregulation. Contemporary advances have decisively shifted the paradigm from bacterial presence to microbial composition and host-microbe interaction, with strain-level variation in *Cutibacterium acnes* and inflammatory signalling networks determining disease expression. While clinical diagnosis remains morphological, effective management increasingly depends on mechanistically targeted, combination therapies, with oral isotretinoin retaining a singular role in severe disease through its multi-pathway effects. The growing threat of antimicrobial resistance mandates disciplined antibiotic stewardship. Importantly, the psychosocial burden of acne elevates it from a cosmetic concern to a condition of substantive clinical consequence. The next era of progress will be defined by precision modulation of the follicular ecosystem - through microbiome engineering, targeted immunotherapies, and AI-based diagnostic systems. With sustained interdisciplinary inquiry, acne vulgaris may be redefined from a chronic relapsing disorder to a biologically regulated disease amenable to durable control.

Declarations

Acknowledgments: The authors declare that Generative AI was used in the creation of this manuscript. ChatGPT-5 was employed for language refinement (improving grammar, sentence structure, and readability of the manuscript) and technical writing assistance (providing suggestions for structuring complex technical descriptions more effectively). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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