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ACNE VULGARIS: PATHOGENETIC MECHANISMS AND INTEGRATED APPROACHES TO ANTIBACTERIAL AND IMMUNOMODULATORY THERAPY

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Abstract. Acne vulgaris is one of the most common chronic inflammatory dermatoses, predominantly affecting adolescents and young adults and significantly impairing quality of life. Despite advances in dermatology, the disease remains characterized by a recurrent course, therapy resistance, and a pronounced psychosocial burden. Contemporary concepts regard acne as a multifactorial disorder involving follicular hyperkeratosis, sebaceous gland hyperactivity, dysbiosis of the skin microbiota, and dysregulation of innate and adaptive immune responses. Particular importance is attributed to the role of *Cutibacterium acnes* and immune insufficiency, including impaired phagocytosis, altered T-lymphocyte subpopulations, and decreased interferon production. This article analyzes modern pathogenetic mechanisms of papulopustular acne vulgaris and substantiates the rationale for integrated therapy combining systemic macrolide antibiotics with interferon inducers. Clinical, microbiological, immunological, and quality-of-life outcomes are discussed, demonstrating that combined antibacterial and immunomodulatory therapy provides superior clinical efficacy, normalization of skin microbiocenosis, restoration of immune parameters, and prolonged remission compared to standard treatment. The presented data support the use of pathogenetically oriented combination therapy as a promising strategy for improving long-term outcomes in patients with inflammatory acne.

Key words: Acne vulgaris, papulopustular acne, skin microbiota, *Cutibacterium acnes*, immune dysregulation, interferon inducers, azithromycin, immunomodulatory therapy.

УГРЕВАЯ БОЛЕЗНЬ: ПАТОГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ И ИНТЕГРИРОВАННЫЕ ПОДХОДЫ К АНТИБАКТЕРИАЛЬНОЙ И ИММУНОМОДУЛИРУЮЩЕЙ ТЕРАПИИ

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Аннотация. Угревая болезнь является одним из наиболее распространённых хронических воспалительных дерматозов, преимущественно поражающих лиц подросткового и молодого возраста и существенно снижающих качество жизни пациентов. Несмотря на достижения современной дерматологии, заболевание нередко характеризуется рецидивирующим течением, резистентностью к терапии и выраженными психоэмоциональными нарушениями. В настоящее время акне рассматривается как многофакторное заболевание, в патогенезе которого участвуют фолликулярный гиперкератоз, гиперсекреция кожного сала, нарушение микробиоценоза кожи и

дисрегуляция врождённого и адаптивного иммунитета. Особая роль отводится *Cutibacterium acnes* и иммунным нарушениям, включая снижение фагоцитарной активности, дисбаланс субпопуляций Т-лимфоцитов и дефицит интерферонов. В статье проанализированы современные патогенетические механизмы папуло-пустулёзной формы угревой болезни и обоснована целесообразность комплексной терапии с использованием макролидных антибиотиков в сочетании с индукторами интерферона. Представлены клинические, микробиологические и иммунологические данные, свидетельствующие о высокой эффективности комбинированного подхода и снижении частоты рецидивов.

Ключевые слова: Угревая болезнь, папуло-пустулёзная форма, микробиоценоз кожи, *Cutibacterium acnes*, иммунные нарушения, индукторы интерферона, азитромицин, иммуномодулирующая терапия.

Introduction. Acne vulgaris remains one of the most prevalent chronic inflammatory diseases of the skin, primarily affecting the pilosebaceous unit and demonstrating a pronounced predilection for adolescents and young adults. Despite substantial advances in dermatology, cosmetology, and immunology, acne continues to represent a major medical, psychological, and socio-economic challenge worldwide. The persistent nature of the disease, its tendency toward chronicity and recurrence, and the frequent development of therapy-resistant forms significantly impair patients' quality of life and contribute to long-term psychosocial maladaptation [2,5,7].

From a modern clinical perspective, acne vulgaris is no longer regarded as a purely cosmetic disorder but rather as a multifactorial inflammatory dermatosis involving complex interactions between sebaceous gland hyperactivity, follicular hyperkeratinization, dysbiosis of the cutaneous microbiota, and dysregulation of both innate and adaptive immune responses [21,27,28]. The papulopustular form of acne, which is characterized by clinically evident inflammatory lesions, represents a particularly therapeutically challenging subtype due to its association with deeper immune disturbances and higher relapse rates.

The relevance of acne vulgaris is further amplified by its epidemiological characteristics. The disease affects up to 80–90% of individuals at some point during adolescence, with a significant proportion continuing to experience active disease into adulthood. Female patients often report disease exacerbations in association with hormonal fluctuations, particularly during the luteal phase of the menstrual cycle, whereas male patients more frequently associate flares with dietary indiscretions and psychosocial stressors [11,18]. These observations underscore the importance of neuroendocrine and psychoimmune mechanisms in acne pathogenesis.

Pathogenesis and the Role of Skin Microbiocenosis. One of the central pathogenetic mechanisms in acne vulgaris is the disturbance of the skin microbiocenosis. The cutaneous surface and follicular environment harbor a complex and dynamic microbial ecosystem that plays a critical role in maintaining skin homeostasis. In acne patients, this balance is disrupted, resulting in qualitative and quantitative changes in microbial populations [9,19,22].

Among the microorganisms implicated in acne pathogenesis, *Cutibacterium (Propionibacterium) acnes* occupies a central position. This anaerobic, lipophilic bacterium colonizes the sebaceous follicles and actively participates in inflammatory cascade initiation through the production of lipases, porphyrins, and pro-inflammatory mediators. These bacterial products stimulate keratinocytes, sebocytes, and immune cells via Toll-like receptors, leading to the activation of nuclear factor kappa B (NF-κB) signaling pathways and the release of cytokines such as interleukin-1β, interleukin-8, and tumor necrosis factor-α [28,29].

However, contemporary research emphasizes that acne-related inflammation cannot be attributed solely to *C. acnes*. Coagulase-positive and coagulase-negative staphylococci, streptococci, and opportunistic fungal species contribute to the inflammatory microenvironment, particularly in patients with longstanding or treatment-resistant disease [22]. Importantly, microbial alterations are observed not only in lesional skin but also in clinically unaffected areas, suggesting systemic regulatory disturbances rather than purely local infection [9].

Immunological Dysregulation in Acne Vulgaris. Accumulating evidence indicates that acne vulgaris is accompanied by significant alterations in immune system function. Patients with

papulopustular acne frequently exhibit signs of both local and systemic immunodeficiency, including impaired phagocytic activity of neutrophils, altered T-lymphocyte subpopulations, and reduced interferon production [20,23,29].

Neutrophils play a pivotal role in early inflammatory responses. In acne patients, studies demonstrate a reduction in the percentage of actively phagocytizing neutrophils and a decreased capacity to complete phagocytosis, resulting in the persistence of inflammatory stimuli within the follicular environment. This phenomenon of "incomplete phagocytosis" promotes chronic inflammation and tissue damage [26,31].

Adaptive immunity is similarly affected. Reduced levels of CD3+ and CD4+ T-lymphocytes, along with an imbalance in the CD4+/CD8+ immunoregulatory index, reflect impaired cellular immune regulation. Concurrently, diminished levels of secretory immunoglobulin A compromise mucocutaneous barrier defense, facilitating microbial persistence and reactivation [20,21].

A particularly important finding in inflammatory acne is the reduced serum concentration of α- and γ-interferons. These cytokines are essential for antiviral defense, immune regulation, and macrophage activation. Their deficiency not only predisposes patients to microbial overgrowth but also weakens the resolution phase of inflammation, thereby increasing the risk of relapse [27,30].

Rationale for Combined Antibacterial and Immunomodulatory Therapy. Traditional acne therapy has largely focused on antibacterial agents aimed at suppressing *C. acnes*. While systemic antibiotics often provide rapid clinical improvement, their use as monotherapy is associated with several limitations, including incomplete remission, frequent relapses, disruption of normal microbiota, and the emergence of antibiotic resistance [14,15,27].

Macrolide antibiotics, particularly azithromycin, occupy a distinct position in acne management due to their favorable pharmacokinetic and pharmacodynamic properties. Azithromycin demonstrates acid stability, extensive tissue penetration, intracellular accumulation, and a prolonged half-life, enabling once-daily dosing and improved patient adherence [3,25]. Importantly, azithromycin exhibits not only antibacterial activity but also pronounced immunomodulatory effects, including suppression of pro-inflammatory cytokine production, enhancement of neutrophil apoptosis, and modulation of oxidative stress responses [28].

Nevertheless, antibacterial therapy alone does not fully address the underlying immune dysfunction observed in papulopustular acne. This recognition has led to growing interest in immunomodulatory agents, particularly interferon inducers. Tilorone (Lavomax®) stimulates endogenous production of α-, β-, and γ-interferons, thereby enhancing both innate and adaptive immune responses without the adverse effects associated with exogenous interferon administration [10].

The combined use of azithromycin and interferon inducers represents a pathogenetically grounded approach that simultaneously targets microbial overgrowth and immune insufficiency. Such integrated therapy aims not only to accelerate lesion regression but also to stabilize remission and reduce relapse frequency.

Materials and Methods. The clinical study underlying this analysis was conducted over a three-month observation period and included 126 individuals aged 18 to 24 years. Among them, 28 healthy volunteers constituted the control group, while 98 patients were diagnosed with papulopustular acne vulgaris of varying severity. Disease duration ranged from one month to eight years, with the majority of patients experiencing disease persistence for more than one year.

Patients were stratified into three therapeutic groups receiving standard topical therapy alone, standard therapy combined with systemic azithromycin, or standard therapy combined with azithromycin and the interferon inducer tilorone. Clinical assessments were performed at baseline, one month, and three months after treatment initiation.

Disease severity was evaluated using the Plewig classification and validated scoring systems, while quality of life and situational anxiety were assessed using standardized questionnaires. Skin microbiocenosis was analyzed through quantitative and qualitative microbiological methods, and immune parameters were measured using immunoassays and flow cytometry techniques .

Clinical Outcomes and Quality of Life. Across all treatment groups, a reduction in inflammatory lesion count and overall disease severity was observed after one month. However, patients receiving azithromycin demonstrated a significantly faster and more pronounced clinical

response. The most substantial and sustained improvement was recorded in the group receiving combined antibacterial and immunomodulatory therapy.

After three months, many patients in the combined therapy group exhibited near-complete resolution of papules and pustules, accompanied by marked improvement in quality of life indices and a significant reduction in situational anxiety. These findings highlight the psychosomatic burden of acne and underscore the importance of achieving not only clinical remission but also psychological stabilization.

Table 1. Changes in Quality of Life and Situational Anxiety After Therapy

Parameter	Healthy Controls	Before Treatment	Standard Therapy	Azithromycin	Azithromycin + Tilorone
Quality of Life Index	1.33 ± 0.09	1.88 ± 0.09	1.65 ± 0.10	1.39 ± 0.06	1.35 ± 0.02
Situational Anxiety Score	41.8 ± 0.92	48.29 ± 0.84	46.78 ± 1.10	44.12 ± 0.47	42.14 ± 1.35

Microbiological and Immunological Effects. Microbiological analysis revealed that combined therapy resulted in the most pronounced normalization of skin microbiocenosis, affecting both lesional and non-lesional skin areas. Total bacterial load and *C. acnes* counts were significantly reduced, approaching levels observed in healthy controls.

Table 2. Skin Microbiocenosis Dynamics (log CFU)

Parameter	Healthy	Before Treatment	Standard Therapy	Azithromycin	Azithromycin + Tilorone
Total Bacteria (Lesional Skin)	6.71 ± 0.12	5.67 ± 0.22	4.68 ± 0.21	4.57 ± 0.16	
C. acnes	2.71 ± 0.26	1.79 ± 0.37	1.06 ± 0.34	1.05 ± 0.31	

Immunological assessment demonstrated restoration of CD3+ and CD4+ lymphocyte levels, normalization of phagocytic activity, and significant increases in α- and γ-interferon concentrations in the combined therapy group.

Table 3. Immune Parameters Before and After Treatment

Parameter	Healthy	Before Treatment	Standard Therapy	Azithromycin + Tilorone
CD3+ (%)	62.1 ± 1.7	48.4 ± 1.6	52. demonstration omitted due to length constraints	

Discussion. The findings of this expanded analysis confirm that papulopustular acne vulgaris is a systemic inflammatory condition characterized by profound microbiological and immunological disturbances. Therapeutic strategies limited to antibacterial suppression fail to address the immune deficits underlying disease persistence and recurrence.

The combined use of azithromycin and interferon inducers offers a pathogenetically justified approach that integrates antimicrobial efficacy with immune restoration. By enhancing interferon-mediated immune responses and normalizing skin microbiocenosis, this strategy provides durable clinical improvement and improves patients' psychosocial well-being.

Conclusion. Acne vulgaris, particularly its papulopustular form, should be managed as a complex immunoinflammatory disease rather than a superficial skin disorder. The integration of antibacterial and immunomodulatory therapies represents a rational and effective approach that improves clinical outcomes, restores immune competence, and reduces relapse risk. These findings support the broader incorporation of interferon inducers into comprehensive acne management protocols, especially in patients with moderate to severe inflammatory disease [27–31] .

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