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The Role of Antibiotic Therapy on Skin Microbial Competition and the Driving Cutibacterium Acnes Resistance

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Abstract. Antibiotics are pervasively integrated into modern life, particularly in dermatological therapeutics, where they have revolutionized the management of cutaneous diseases while concurrently posing significant risks. Although existing research has partially demonstrated the detrimental effects of excessive or prolonged antibiotic use, the ecological consequences of antibiotic therapy on skin microbial competition dynamics remain substantially underexplored. Therefore, this systematic review critically examines the impact of antibiotic treatment on acne vulgaris through three interconnected lenses: the disruption of inter-microbial competitive mechanisms within the skin microbiota, the development and ramifications of antimicrobial resistance, and the resultant adverse clinical outcomes. By synthesizing current evidence across these domains, this review elucidates the complex interplay between antibiotic intervention, microbial ecology, and disease pathogenesis in acne. This comprehensive analysis holds significant implications for refining therapeutic strategies towards more ecologically sustainable acne management and provides a crucial conceptual foundation for the development of novel, microbiome-preserving treatment modalities.

Keywords: Antibiotic Resistance, Skin Microbiome, Cutibacterium acnes, Microbial Competition

1. Introduction

The human skin microbiome is a complex ecosystem composed of Staphylococcus, Cutibacterium, Corynebacterium, and other taxa that engage in intricate ecological interactions [1]. Ecological interactions among cutaneous microorganisms exhibit competitive dynamics characterized by reciprocal suppression. For example, Staphylococcus epidermidis has been shown to produce novel antimicrobial peptides that inhibit Staphylococcus aureus colonization [2]. Acne vulgaris, a chronic inflammatory disorder of the pilosebaceous unit, has been linked to cutaneous dysbiosis, particularly the overgrowth of C. acnes [3]. Consequently, antibiotic therapy remains a mainstay of clinical acne management. However, indiscriminate antibiotic use has precipitated significant clinical challenges, with approximately 60% of clinical C. acnes isolates demonstrating resistance to commonly prescribed macrolide antibiotics [4].

Beyond resistance emergence, antibiotic therapy may also disrupt ecological competition within the skin microbiota, eliminating commensal species that normally suppress pathogen overgrowth.

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Despite growing recognition of antibiotic resistance as a global health crisis, the ecological consequences of antibiotic therapy on cutaneous microbial competition remain insufficiently investigated. This review explores how antibiotic therapy disrupts competitive microbial interactions on the skin, with a focus on the mechanisms through which such disruption facilitates the selection and persistence of resistant C. acnes populations. Therefore, elucidating these mechanisms is critical not only for mitigating antimicrobial resistance but also for guiding the development of ecologically informed therapeutic strategies that preserve microbiome integrity and enhance long-term treatment efficacy.

2. Disruption of cutaneous microbial competition by antibiotics

Under physiological conditions, the skin microbiome maintains a dynamic equilibrium through continuous mutual competition among commensal species. This balance is primarily governed by three key competitive mechanisms: niche occupation, nutrient competition, and antagonistic molecule production [5]. However, the indiscriminate application of topical antibiotics disrupts this delicate ecosystem by non-selectively eliminating commensal bacteria, thereby dismantling these critical competitive barriers. Consequently, this disruption creates an ecological vacuum that facilitates the expansion of antibiotic-resistant pathogens such as Staphylococcus aureus and virulent strains of Cutibacterium acnes.

SanMiguel et al. provided experimental evidence for the collapse of niche competition following antibiotic intervention [6]. In a controlled trial with 22 healthy adults, four 5×5 cm test areas were demarcated on each participant's forearm and treated twice daily for seven days with either mupirocin ointment, 2% chlorhexidine, petroleum jelly (vehicle control), or left untreated (blank control). Microbial analysis over a 28-day follow-up revealed a significant reduction ($p < 0.01$) in commensal Staphylococcus epidermidis and Corynebacterium spp. from days 3 to 7 post-treatment in the antimicrobial groups. This reduction effectively eliminated key competitors of S. aureus. Subsequent co-culture experiments demonstrated that S. aureus exhibited a 2-4-fold increase in growth when paired with microbiota from treated skin versus controls ($p < 0.001$), likely due to the absence of bacteriocin-producing commensals. These findings collectively demonstrate that broad-spectrum antimicrobials inadvertently create permissive conditions for S. aureus colonization by simultaneously depleting two major competitive bacterial groups: coagulase-negative Staphylococci and Corynebacterium species.

The disruption of nutrient competition and antagonistic molecule production was similarly demonstrated in a clinical trial by Niedźwiedzka et al. [7]. This study enrolled 78 patients with mild-to-moderate acne who were randomized to receive either topical 1% clindamycin plus 0.025% retinoic acid, oral doxycycline (100 mg/day), or placebo for eight weeks. Clindamycin reduced total bacterial load by 1.9 $\log_{10}$CFU/cm², while doxycycline reduced it by 1.4 $\log_{10}$CFU/cm². Notably, the prevalence of the lugdunin gene—encoding an anti-S. aureus peptide—decreased from 92% to 12% among S. aureus isolates after treatment. In vitro assays revealed that the inhibition zone of S. aureus strain A9 against C. acnes RT5 narrowed from 10.3±0.8 mm at baseline to less than 2 mm ($p < 0.0001$). Concurrently, gas chromatography-mass spectrometry detected a 2.1-fold increase in free palmitic acid (C16:0) in the clindamycin group ($p < 0.01$), indicating reduced lipid consumption by commensals. In these lipid-rich conditions, C. acnes RT5 exhibited enhanced pathogenicity, forming biofilms 1.7 times thicker than baseline.

While these studies provide compelling correlative evidence, several methodological limitations warrant consideration. SanMiguel et al.'s study was limited by small sample size (n=22), short duration (28 days), and anatomical restriction (forearm), limiting the generalizability to broader skin

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microenvironments [6]. Niedźwiedzka et al.'s trial, while more clinically relevant, contained confounding variables—including concurrent retinoid use and systemic antibiotic effects—that preclude causal attribution to antibiotic effects alone [7]. To address these gaps, future investigations should employ longitudinal, site-specific designs that simultaneously monitor niche occupation, nutrient metabolism, and interspecies antagonism following targeted antibiotic interventions. Multi-omics approaches—including metagenomic sequencing (for niche occupancy assessment), metabolomic profiling (for nutrient competition analysis), and transcriptomic characterization of antimicrobial peptide expression. Additionally, incorporating spatial transcriptomics would further clarify the spatial dynamics between commensal and pathogenic species within the skin's microarchitecture.

3. Direct driving of cutibacterium acnes drug resistance by antibiotics

The overuse of antibiotics exerts selective pressure on Cutibacterium acnes, accelerating the emergence of resistant strains through a multifactorial process involving genetic selection, mutation, HGT, and clonal expansion (reference). Rather than merely selecting pre-existing resistant variants, antibiotics at subinhibitory or therapeutic concentrations can actively induce genetic mutations, facilitate the horizontal transfer of resistance determinants, and promote the fixation of resistant mutants. These dynamics establish a self-reinforcing cycle of "selection-mutation-transfer-fixation" that propels the evolution of antimicrobial resistance. From an evolutionary perspective, such selection pressure favors bacterial phenotypes that enhance survival under drug exposure, gradually reshaping population genetics, in which more outstanding individuals are favored during the selection process. High selection pressure means that only the most outstanding individuals are allowed to reproduce, while low selection pressure gives even relatively poor individuals the opportunity to contribute offspring [8].

Leyden & Levy observed a global rise in macrolide-resistant C. acnes strains, including among antibiotic-naïve individuals [9]. The authors attributed this to prolonged monotherapy—specifically ≥8 weeks of topical 1% clindamycin ($P < 0.01$) or ≥12 weeks of oral tetracycline/doxycycline. Although resistance levels initially declined during treatment, they rebounded within six months after discontinuation. Agar dilution assays confirmed that resistant strains exhibited minimum inhibitory concentrations (MICs) of ≥8 mg L^{-1} for erythromycin and ≥4 mg L^{-1} for clindamycin, far exceeding the clinical breakpoint of 0.5 mg L^{-1}. Notably, adjunctive benzoyl peroxide significantly reduced resistance emergence, underscoring the role of sustained selection gradients within the pilosebaceous unit in maintaining resistant subpopulations.

The genetic basis of resistance has been further characterized by Beirne et al., who analyzed three multidrug-resistant (MDR) strain isolates from patients unresponsive to standard therapy [10]. Strains CA39 (erythromycin MIC >256 mg L^{-1}; clindamycin MIC 64 mg L^{-1}; tetracycline-sensitive), CA51 (erythromycin/clindamycin MIC >256/128 mg L^{-1}; tetracycline MIC 32 mg L^{-1}), and CA17 (resistant to erythromycin, clindamycin, and moxifloxacin, MICs >32 mg L^{-1}) exhibited distinct resistance profiles and underwent whole-genome sequencing. CA39 harbored a 23S rRNA S101L mutation, CA51 possessed both S101L and the erm(X) gene, and CA17 exhibited G2057A plus erm(X). Tetracycline resistance in CA51 and CA17 was mediated by tet(K) (encoding an efflux pump) and tet(M) (a ribosomal protection protein). Additionally, CA17 exhibited fluoroquinolone resistance via gyrA (E761R) and parC (S79F) mutations. Critically, erm(X) and tet(K) were plasmid-borne, underscoring horizontal gene transfer (HGT)'s role in disseminating MDR traits.

Despite these insights, both studies exhibit limitations. The clinical dataset lacked genomic resolution and failed to distinguish between topical and systemic regimens. The genomic study was

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limited by a small sample size (n = 3), constraining generalizability. To address these gaps, future research should adopt longitudinal, large-scale designs that track resistance emergence over time and across treatment types. Collectively, the evidence confirms that antibiotic use drives C. acnes resistance via selection-mutation-transfer-fixation dynamics, necessitating judicious antimicrobial stewardship and combinatorial therapies to mitigate resistance evolution.

4. Clinical impact and microecological restoration strategies

The protracted use of antibiotics for acne management exerts profound clinical consequences extending far beyond the well-documented disruption of cutaneous microbial interspecies competition (dysbiosis) and the development of AMR. Significant systemic and organ-specific adverse effects pose substantial risks, compelling a critical reassessment of prolonged treatment regimens. Compelling empirical evidence underscores these concerns.

Bhate et al. conducted a pivotal large-scale cohort study investigating these systemic risks [11]. Their analysis encompassed 118,496 acne patients aged 12-25 years initiating their first course of oral tetracycline-class antibiotics (doxycycline, lymecycline, minocycline) for ≥28 days. Participants were stratified based on treatment duration: those receiving therapy for ≥12 weeks constituted the long-duration exposure group, while those treated for <12 weeks served as the control group. The findings revealed alarming increases in the risk of specific bacterial infections associated with extended antibiotic use:

(1) Group A Streptococcal (GAS) Pharyngitis: The incidence rate of GAS pharyngitis was significantly elevated in the long-duration group (12.4 per 1000 person-years) compared to the control group (7.5 per 1000 person-years). After adjusting for confounding variables, the hazard ratio (HR) was 1.65 (95% CI 1.52–1.79). This translates to an excess of 3.9 cases of GAS pharyngitis per 1000 person-years attributable to prolonged therapy. Critically, a dose-response relationship was evident: each additional 4 weeks of antibiotic exposure increased the HR by a further 6% (p-trend < 0.001).

(2) Methicillin-Resistant Staphylococcus aureus (MRSA) Skin and Soft Tissue Infections (SSTIs): The incidence of MRSA-associated SSTIs more than doubled in the long-duration group (2.1 per 1000 person-years) versus the control group (0.9 per 1000 person-years). The adjusted HR was 2.31 (95% CI 1.87–2.85), equating to an excess of 1.4 MRSA-SSTI cases per 1000 person-years. This heightened risk peaked within the first 12 months after antibiotic cessation and gradually declined thereafter, though it persistently remained above baseline levels.

(3) Hospitalization-Requiring Bacterial Infections: The incidence of serious bacterial infections necessitating hospitalization was also higher in the long-duration group (1.8 per 1000 person-years) compared to controls (1.2 per 1000 person-years).

Collectively, Bhate et al.'s data robustly demonstrate that protracted tetracycline use not only facilitates increased cutaneous MRSA colonization but also significantly elevates the risk of invasive GAS infections and serious systemic bacterial infections requiring hospital care, posing a clear threat to patient health.

Beyond these systemic infectious complications, long-term antibiotic therapy is also intrinsically linked to suboptimal acne treatment outcomes, including an increased propensity for scarring—a major determinant of long-term morbidity and psychosocial impact. Gang et al. (2021) specifically investigated this scarring risk in a cohort study of 403 female patients (aged 18-45 years) with moderate-to-severe acne (Investigator's Global Assessment [IGA] ≥3). Patients were categorized based on antibiotic treatment duration: short-course (≤90 days, n=138), medium-course (91-180 days, n=147), and long-course (>180 days, n=118). The analysis revealed a striking, duration-

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dependent escalation in scarring prevalence: Short-course group: Scarring incidence = 18.9% (Reference group; adjusted Odds Ratio [aOR] = 1.0); Medium-course group: Scarring incidence = 29.3% (aOR = 1.72, 95% CI 1.05–2.83). This corresponded to an excess of +1.9 scarring events per 100 person-years for every additional 30 days of therapy; long-course group: scarring incidence = 41.7%. The risk further increased, yielding an excess of +3.2 scarring events per 100 person-years for every additional 30 days of therapy.

The overarching trend indicated that each 30-day extension in antibiotic treatment duration was associated with an 11% increase in the odds of scarring (p-trend = 0.003). The burden was particularly severe in specific high-risk subgroups: patients with nodulocystic acne in the long-course group exhibited a scarring rate of 52.4%, and those experiencing delayed escalation to isotretinoin (>12 months) had a scarring rate of 46.8%. These data systematically demonstrate that prolonged antibiotic courses correlate strongly with more severe scarring, directly contributing to treatment failure by allowing disease progression and permanent tissue damage.

The studies by Bhate et al. and Garg et al. provide complementary, robust evidence of the significant harms associated with long-term antibiotic therapy for acne [11, 12]. Bhate et al. primarily highlight the increased risks of systemic and cutaneous infections (GAS, MRSA, serious bacterial infections) and the contribution to the AMR crisis. In contrast, Garg et al. emphasize the detrimental impact on core treatment efficacy, manifesting as increased scarring—a primary concern for patients. Crucially, both studies identified a consistent, statistically significant linear dose-response relationship between increasing duration of antibiotic exposure and escalating risk (HR for infection, OR for scarring). This compellingly establishes prolonged antibiotic use as a major modifiable risk factor for these adverse outcomes.

While highly informative, both studies possess inherent limitations. Bhate et al. relied on healthcare database records, potentially introducing misclassification bias in outcome measurement (e.g., infection diagnosis codes) and limited data on potential confounders. Garg et al.'s cohort was restricted to females, limiting generalizability [12]. The substantial adverse effects documented—ranging from increased serious infections and AMR promotion to treatment failure and disfiguring scarring—underscore the urgent need to minimize the duration of systemic antibiotic use in acne management and to develop effective, ecologically sound therapeutic alternatives. Promising strategies actively under investigation aim to preserve or restore a healthy skin microbiome while effectively treating acne, such as Skin Microbiome Transplantation, Bacteriophage (Phage) Therapy, Prebiotic, Probiotic, and Postbiotic Strategies, and so on [13]. This will alleviate the significant risks currently clearly associated with the long-term antibiotic use recorded by Bhate, Garg, and others.

5. Conclusion

Antibiotic therapy represents a quintessential double-edged sword in dermatological practice, particularly for conditions like acne. Judicious, short-term use delivers undeniable therapeutic benefits, effectively mitigating inflammation and bacterial proliferation central to acne pathogenesis. Conversely, as comprehensively documented in the preceding analysis, protracted antibiotic administration inflicts substantial and often underestimated iatrogenic damage. This manifests primarily through: Profound Microbiome Disruption, Accelerated Antimicrobial Resistance, Treatment Failure and Sequelae. Therefore, the cumulative evidence mandates a decisive paradigm shift away from reliance on prolonged, broad-spectrum antimicrobial suppression. The future of effective and sustainable acne management necessitates a transition towards Precision Microbiome Engineering. This innovative framework aims to overcome the inherent limitations and dangers of conventional antibiotics by developing targeted strategies—such as bacteriophage therapy, microbial

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transplantation, or microbiome modulators (prebiotics, probiotics, postbiotics)—that selectively correct dysbiosis while preserving ecological integrity and minimizing collateral damage. These approaches leverage ecological principles to suppress pathogens while reinforcing beneficial commensals, thereby restoring homeostasis rather than indiscriminately eradicating microbial communities. Furthermore, integrating personalized treatment based on individual microbiome profiles could enhance efficacy and prevent recurrence. Only through such precision approaches can we effectively address the multifaceted challenges posed by long-term antibiotic use, ultimately leading to more sustainable, effective, and safer dermatological care that aligns with both clinical goals and microbiological stewardship.Future research should prioritize large-scale clinical trials to validate these novel interventions, alongside developing clear guidelines for their integration into standard care. Finally, fostering collaboration between dermatologists, microbiologists, and bioengineers will be crucial to usher in this new era of ecologically informed, patient-specific acne therapeutics, transforming a classical treatment dilemma into an opportunity for innovation and improved global skin health.

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