

ORIGINAL ARTICLE

Hidradenitis suppurativa skin microbiome: In-depth analysis and modulation by systemic therapies

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Abstract

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease with a multifactorial pathogenesis involving genetic, lifestyle and microbial factors. While cutaneous microbiome shifts have been reported for this disease, the impact of systemic immunomodulators and antibiotics on HS microbiome remains poorly defined.

Objective: To characterize species-level cutaneous dysbiosis in HS and evaluate the effects of three standard-of-care systemic therapies, clindamycin/rifampicin (ATB), adalimumab (ADA) and secukinumab (SEC) on skin microbial composition.

Methods: We performed 16S rRNA sequencing on 251 skin swabs from lesional and non-lesional sites of 52 HS patients and 31 healthy matched controls. In a sub-cohort of 28 patients, microbial shifts were evaluated following 12 weeks of therapy with ATB ($n=8$), ADA ($n=12$) and SEC ($n=8$).

Results: HS skin exhibited profound dysbiosis defined by the depletion of homeostatic commensals (*Cutibacterium acnes*, *Staphylococcus hominis*, *S. epidermidis*) and a synergistic expansion of anaerobic pathogens, primarily Gram-positive anaerobic cocci (GPAC; *Finegoldia magna*, *Peptoniphilus grossensis* and *Fenollaria massiliensis*), *Lawsonella clevelandensis* and *Campylobacter ureolyticus*. A 13-taxa microbial signature accurately discriminated the HS phenotype (AUC=0.92). Following 12 weeks of treatment, ATB markedly attenuated dysbiosis by reducing pathogen loads and significantly increasing microbial richness. In contrast, ADA and SEC did not alter pathogen abundance and were associated with a slight decline in protective commensals.

Conclusions: Systemic antibiotics partially restore cutaneous microbiome homeostasis in HS by targeting anaerobic pathogens while preserving beneficial commensals, an effect not observed with the tested biologics. These findings highlight the need for microbiome-directed adjuvant therapies to complement immunomodulation in HS management.

KEYWORDS

adalimumab, clindamycin and rifampicin, hidradenitis suppurativa, microbiota, Secukinumab

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INTRODUCTION

Hidradenitis suppurativa (HS), or acne inversa, is a chronic, debilitating inflammatory skin disease primarily affecting the axillary, inguinal and genitoanal region.¹ It is characterized by deep-seated, painful nodules, abscesses and sinus tracts (fistulae) that lead to dermal scarring and malodorous discharge.¹ HS imposes a severe psychological toll, leading to depression, social isolation and susceptibility to addictive behaviour.² While the exact primary trigger of HS remains a subject of intense investigation, the current consensus points towards a complex, multifactorial aetiology involving genetic susceptibility, lifestyle triggers, immune dysregulation and cutaneous microbial dysbiosis.^{3–5} Familial cases have been linked to mutations in the γ -secretase complex (*NCSTN*, *PSENEN* and *PSEN1*), suggesting impaired follicular homeostasis via altered Notch signalling.⁶ Additionally, obesity and tobacco smoking are thought to promote follicular occlusion and hyperkeratosis, leading to the rupture of the pilosebaceous unit.^{4,7} The histopathological progression of HS follows a three-stage cascade: (i) follicular occlusion due to keratosis and epithelial hyperplasia; (ii) follicular rupture, which releases pro-inflammatory microbial- and damage-associated molecular patterns into the dermis, triggering a robust immune response; and (iii) the establishment of chronic inflammation, leading to abscesses and sinus tracts. These structures provide a niche for biofilm-producing bacteria, fuelling persistent inflammation and purulent drainage.^{8–10} The immunological landscape of HS shows an aberrant activation of the innate immune response, characterized by a Th1/Th17-dominant milieu and the upregulation of TNF- α , IL-1 β , IL-6 and the IL-12/IL-23/IL-17 axis.^{11,12} Despite a compensatory increase in antimicrobial peptides and β -defensins, the pro-inflammatory milieu persists, signalling a breakdown in host-microbe homeostasis.¹³ In line with this, recent studies have reported significant microbial shifts in HS lesions, marked by the expansion of pathobionts such as *Porphyromonas*, *Peptoniphilus* and *Prevotella* species.^{14,15} Current management of moderate-to-severe HS includes treatment with clindamycin/rifampicin (ATB) for its antimicrobial and immunomodulatory properties.¹⁶ When antibiotics fail to achieve disease control, the TNF- α antagonist adalimumab (ADA) or the IL-17A antagonist secukinumab (SEC) are deployed, both having demonstrated efficacy in pivotal phase III trials.^{17–19} However, it remains unclear whether these systemic therapies correct the underlying microbial dysbiosis or merely dampen the host's inflammatory response to a persistent microbial trigger.²⁰ In this study, we provide an in-depth characterization of the HS skin microbiome and compare the microbial modulatory effects of three standard-of-care systemic therapies: ATB, ADA and SEC. By analysing the shifts in both lesional and non-lesional skin over 12 weeks of treatment, we aim to determine if microbial restoration is a prerequisite for clinical improvement and to identify bacterial signatures that may predict therapeutic success.

Why was the study undertaken?

- While cutaneous microbiome shifts are documented in hidradenitis suppurativa, the impact of systemic immunomodulators and antibiotics on the HS microbiome remains poorly defined. This study was undertaken to achieve an in-depth characterization of cutaneous dysbiosis in HS and evaluate for the first time, the effects of three standard-of-care systemic therapies, namely clindamycin/rifampicin, adalimumab and secukinumab, on HS skin microbial composition.

What does this study add?

- This study reveals that HS skin exhibits a profound dysbiosis defined by the depletion of homeostatic commensals and a synergistic expansion of anaerobic pathogens that correlates with disease severity and chronicity. Furthermore, we identified a 13-taxa microbial signature that accurately discriminates the HS phenotype. Finally, our longitudinal evaluation of three systemic therapies showed that while antibiotics successfully reverse dysbiosis, the tested biologics were unable to address the microbial component of the disease.

What are the implications of this study for disease understanding and/or clinical care?

- These findings introduce a vital paradigm, revealing that clinical healing in hidradenitis suppurativa does not equate to cutaneous ecological recovery. Because immunomodulatory biologics leave the pathogenic consortium intact, targeted antimicrobial intervention remains a therapeutic requirement. These data suggest that future therapeutic strategies should integrate antimicrobial or ecobiotic interventions alongside immunomodulation to achieve sustained clinical remission and ultimately prevent the recurrence of lesional activity.

MATERIALS AND METHODS

Study population and clinical assessment

HS patients and age-/sex-matched healthy controls (HCs) were enrolled at the Department of Dermatology and Allergology, Technical University of Munich (Approval n. 580/16S). All participants were of Caucasian ethnicity. Disease severity was assessed via Hurley staging (Figure 1a)²¹ and the International Hidradenitis Suppurativa Severity Score System (IHS4).²² To characterize the microbiome, skin swabs were collected from axillary and inguinal

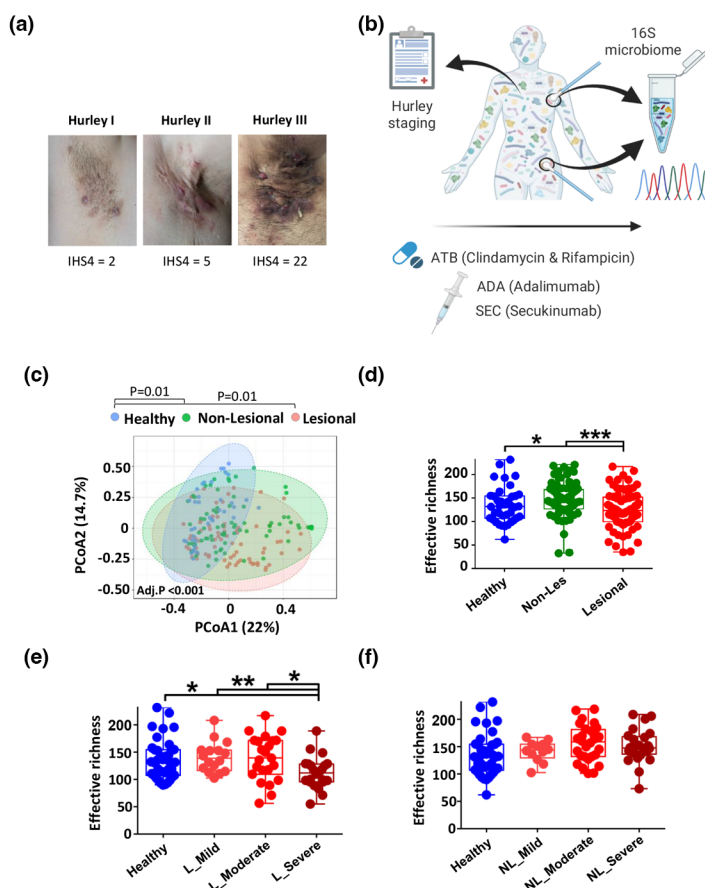


FIGURE 1 Hidradenitis suppurativa is associated with significant cutaneous dysbiosis and a profound loss of microbial α -diversity. (a) Representative clinical photographs of axillary skin across varying HS severity grades. (b) Schematic of the sampling procedure and longitudinal study design. (c) Principal Coordinates Analysis (PCoA) plot of β -diversity (Bray-Curtis/Unifrac) demonstrating a significant divergence in microbial community structure between HS patients and healthy controls. (d) Box plot illustrating a significant loss of microbial richness (observed ASVs/species) in HS skin. (e, f) Microbial richness stratified by clinical severity index in (e) lesional and (f) non-lesional HS skin. Horizontal lines in box plots represent the median, with whiskers indicating the interquartile range. Statistical significance was determined using Kruskal-Wallis tests for multi-group comparisons with p -values adjusted using the Benjamini-Hochberg procedure. The asterisks indicate statistically significant differences and correspond to * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. Data derived from cutaneous microbiome swabs of HS predilection sites in HS patients ($n = 52$) and healthy controls ($n = 31$).

sites of 52 HS patients and 31 HCs. A total of 251 skin swabs were analysed in this study, comprising 173 baseline samples (68 lesional, 67 non-lesional and 38 healthy controls) and 78 post-treatment samples (39 lesional and 39 non-lesional). Baseline cross-sectional analyses were restricted to pre-treatment samples. A sub-cohort of 28 patients with moderate-to-severe HS was followed longitudinally during 12 weeks of systemic therapy with clindamycin/rifampicin (ATB, $n = 8$; 300 mg each, twice a day), adalimumab (ADA, $n = 12$; standard 160/80/40 mg dosing), or secukinumab (SEC, $n = 8$; 300 mg weekly for 5 weeks, then every 4 weeks). Swabs were collected at baseline and week 12 (Figure 1b) according to Human Microbiome Project guidelines,²³ with participants refraining from showering for 24 h prior to sampling. Exclusion criteria included the use of topical corticosteroids within 3 days or systemic antibiotics/corticosteroids within 4 weeks prior to sampling. HCs were defined by the absence of chronic skin disorders and no systemic antibiotic use within the preceding 6 months.

Specimen collection and DNA extraction

Skin swabs were collected from HS lesions, non-lesional skin (5–10 cm from lesions) and matched HC sites using forensic 4N6FLOQ swabs (COPAN) pre-moistened with 0.15 M NaCl/0.1% Tween-20. To ensure adequate biomass recovery, sites were swabbed back and forth approximately 50 times with firm pressure. Total microbial DNA was extracted using the QIAamp DNA Microbiome Kit (Qiagen), which includes an enzymatic host-DNA depletion step to enrich for viable microbiota.²⁴ Extracted DNA samples were stored at -30°C until further processing.

16S rRNA gene amplification and sequencing

Microbial diversity was analysed by 16S rRNA gene amplicon sequencing targeting the V3-V4 regions using universal primers.²⁵ Sequencing libraries were prepared

via a two-step PCR protocol: an initial amplification of the target region followed by an indexing PCR to attach Illumina adapters (Nextera XT Index Kit v2). Purified libraries were quantified using the QuantiFluor dsDNA System (Promega) and pooled equimolarly after quality assessment on a Qsep1+ Bio Fragment Analyser. The final pool was sequenced on an Illumina MiSeq platform (2×300 bp paired-end reads) with a 10% PhiX spike. Negative controls were included throughout the workflow to monitor for background contamination.

16S reads downstream processing and statistical analyses

Raw 16S rRNA gene sequences were processed using the UPARSE method²⁶ via the IMNGS platform.²⁷ High-quality reads were clustered into amplicon sequence variants (ASVs) and taxonomically assigned using the RDP classifier.²⁸ Our workflow was previously optimized using mock communities, enabling accurate taxonomic identification at the species level (99% sequence similarity).²⁴ Statistical analyses were performed in R via the Rhea pipeline.²⁹ Confounding variables (site, sex, age) were corrected using ComBat.³⁰ Statistical noise was minimized by applying a prevalence cut-off of 0.25% and an abundance cut-off of 0.5%. β -diversity was assessed using generalized UniFrac distances and PERMANOVA. Differential abundance was determined using Kruskal-Wallis and Mann-Whitney *U* tests. Biomarker discovery was conducted using Linear Discriminant Analysis Effect Size (LEfSe).³¹ Microbial interactions were modelled using Spearman correlations and the SparCC algorithm.³² *p*-values were adjusted using the Benjamini-Hochberg procedure. Detailed clinical protocols and experimental methods are provided in the [Supporting Information](#).

RESULTS

Skin dysbiosis and a profound loss of microbial diversity characterize HS lesions

To investigate the role of cutaneous dysbiosis in HS, we analysed 251 skin swabs from 52 HS patients and 31 healthy controls (HC) (Table 1) via 16S rRNA gene sequencing. The analysis yielded 7.12×10^6 filtered reads (averaging 2.84×10^4 reads per sample), identifying 3496 amplicon sequence variants (ASVs) across 3 dominant phyla, 39 genera and 144 species. Baseline β -diversity analysis using Principal Coordinate Analysis (PCoA) revealed significantly distinct microbial compositions in HS lesional skin compared to healthy controls, with non-lesional skin occupying an intermediate position (Figure 1c). Pairwise comparisons confirmed that all groups differed significantly (Figure S1), with a substantial reduction in microbial richness exclusively observed in HS

TABLE 1 General characteristics of the cohort.

	Control	HS-Patients
Age (years)	37.6 ± 11	38 ± 11
Gender	14F, 17M	22F, 30M
IHS4	NA	17 ± 11
Nodule count	NA	5.96 ± 3.53
Abscess COUNT	NA	1.85 ± 2.52
Draining fistulae	NA	1.37 ± 1.72
Disease duration (years)	NA	9 ± 7

lesions (Figure 1d). Furthermore, stratification by disease severity (IHS4) demonstrated that this loss of richness was restricted to severe lesional skin, whereas mild-to-moderate and non-lesional skin maintained diversity levels comparable to controls (Figure 1e,f).

Taxonomic analysis at the phylum level revealed a significant increase in *Pseudomonadota* (formerly *Proteobacteria*), progressing from healthy to non-lesional skin and peaking in HS lesions. *Bacillota* (formerly *Firmicutes*) and *Actinomycetota* (formerly *Actinobacteria*) dominated both healthy and diseased skin, with no significant differences in their relative abundances (Figure S2a,b). Heat tree analysis at the genus level identified a significant enrichment of Gram-positive anaerobic cocci (GPAC; *Finegoldia*, *Peptoniphilus* and *Fenollaria*), *Lawsonella* and *Campylobacter* in HS lesions. Conversely, healthy and non-lesional sites were enriched in *Cutibacterium*, *Staphylococcus*, *Micrococcus*, *Kocuria* and *Moraxella* (Figure 2a). Dot plots of relative abundances corroborate these shifts, showing a significant increase in GPAC, *Lawsonella*, *Campylobacter* and *Anaerococcus* in HS lesions (Figure 2b). Notably, this expansion was paralleled by a depletion of the commensals *Staphylococcus* and *Cutibacterium*. Non-lesional HS skin was characterized by the expansion of *Corynebacterium* and *Kocuria* (Figure 2c,d, Figure S2c).

Notably, site-specific microbial signatures (axillary vs. inguinal) were only preserved in healthy controls ($p < 0.002$). In HS, both lesional and non-lesional skin exhibited a loss of topographical variation, suggesting that the disease pathology overrides the ecological influence of local microenvironments (Figure S3a). In healthy controls, these differences were driven by the preferential growth of *Cutibacterium* in the inguinal region and *Peptoniphilus* in the axilla (Figure S3b). Biological sex did not drive noticeable microbial variation (Figure S4a,b).

HS dysbiosis shows an expansion of anaerobes at the cost of protective commensals

To further elucidate the role of the cutaneous microbiome in HS, we performed a high-resolution taxonomic analysis at the species level (99% sequence similarity). HS lesions were heavily colonized by the GPAC members *Finegoldia*

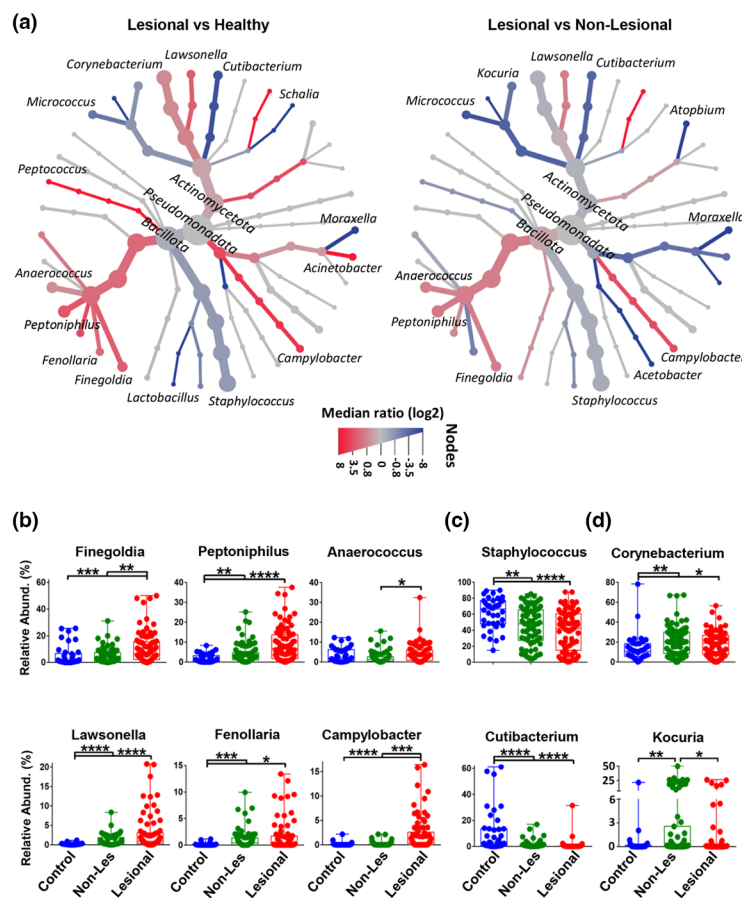


FIGURE 2 Differential taxonomic abundance of HS lesional versus non-lesional and healthy skin at genus level. (a) Heat tree analysis illustrating the differential abundance of taxa in HS lesional skin (red) compared to healthy or non-lesional skin (blue). Node size and colour intensity reflect the magnitude of enrichment and statistical significance, respectively. (b–d) Dot plots representing the relative abundance at the genus level for (b) opportunistic pathogenic taxa enriched in HS lesions (c) key commensal taxa dominating healthy controls and (d) taxa prevalent in non-lesional HS skin. Box plots represent the median and interquartile range. Statistical significance for abundance plots was determined using Kruskal-Wallis tests for multi-group comparisons with p -values adjusted using the Benjamini-Hochberg procedure. The asterisks indicate statistically significant differences and correspond to * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. Healthy controls ($n = 31$); HS patients ($n = 52$).

magna, *Fenollaria massiliensis*, *Peptoniphilus grossensis* and *P. lacrimalis*, alongside *Lawsonella clevelandensis*, *Corynebacterium simulans* and *Campylobacter ureolyticus*. Notably, *S. aureus* was detected in 37% of HS patients, exceeding 30% relative abundances in several cases (Figure 3a). Conversely, diseased skin showed a marked depletion of potentially beneficial commensals, specifically *Staphylococcus epidermidis*, *S. hominis* and *Cutibacterium acnes* as well as *Staphylococcus caprae*, *Corynebacterium ureicelerivorans* and *Anaerococcus octavius* (Figure 3b). Interestingly, the relative abundances of *Corynebacterium tuberculostearicum* and *Kocuria rhizophila* were particularly increased on non-lesional HS (Figure 3c).

LEfSe analysis identified *S. hominis*, *C. acnes* and *S. epidermidis* as the primary biomarkers for healthy skin ($\text{LDA} > 4.7$, $p < 0.001$), both in comparison to lesional (Figure 3d) and non-lesional HS (Figure 3e). Conversely, HS lesions were strongly associated with *F. magna*, *C. simulans* and *P. grossensis* ($\text{LDA} > 4.2$, $p < 0.001$; Figure 3d). The non-lesional skin exhibited a distinct signature characterized by

C. simulans and *Acinetobacter plantarum* when compared to healthy controls (Figure 3e), and retained a stronger association with *S. hominis* and *A. plantarum* relative to HS lesions (Figure 3f). Together, these findings demonstrate a significant taxonomic shift in HS, where a specialized anaerobic consortium systematically replaces protective commensals. The depletion of *S. hominis* and *C. acnes*, paired with pathogenic expansion, underscores a state of profound dysbiosis.

Key members of the HS skin microbiota strongly correlate with disease severity and duration

To evaluate the clinical relevance of the HS microbiota, we performed correlation and machine learning analyses on the 13 most significantly regulated taxa. Spearman analysis revealed that pathogens, primarily GPAC members (*P. grossensis*, *P. lacrimalis*, *F. magna*, *F. massiliensis*), *C. ureolyticus*, and *L. clevelandensis*, correlated positively with IHS4 severity scores and disease duration. Conversely,

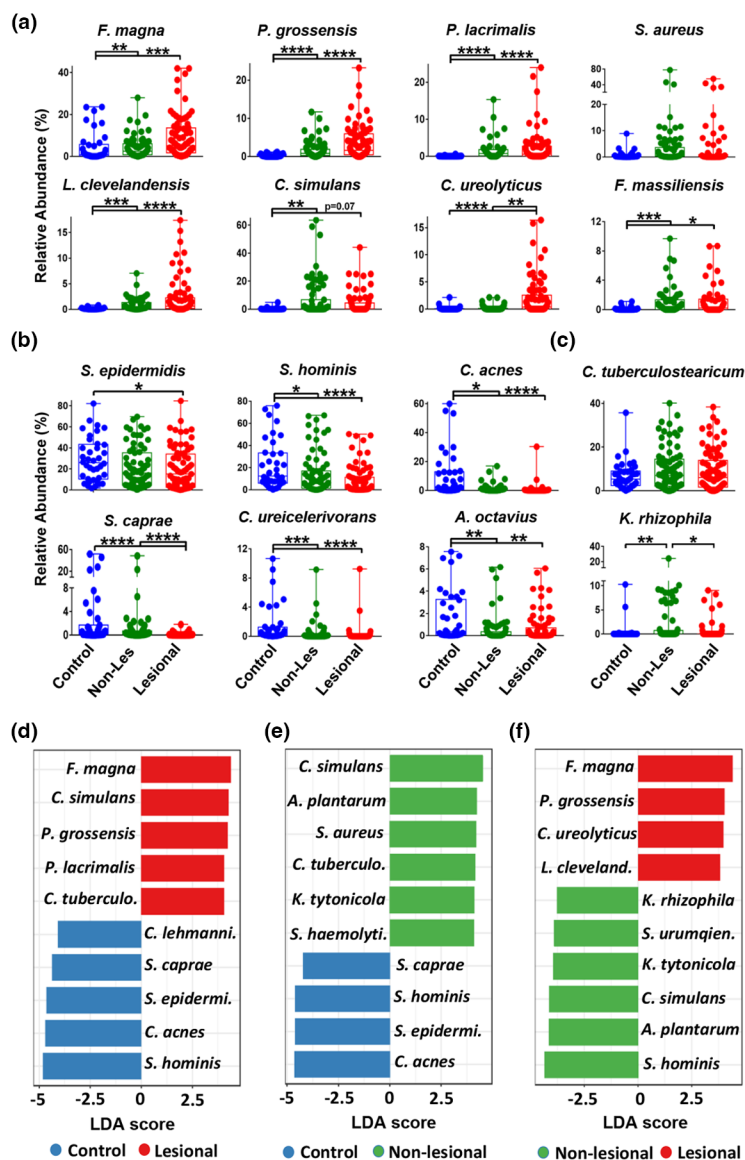


FIGURE 3 Species-level characterization of HS skin reveals an expansion of anaerobes at the cost of protective commensals. (a) Relative abundance of key opportunistic pathogens associated with HS lesions. (b) Relative abundance of dominant skin commensals at the species level. (c) Taxa prevalent in non-lesional HS skin. (d–f) Linear Discriminant Analysis Effect Size (LEfSe) identifying discriminative taxonomic biomarkers in lesional HS compared to healthy and non-lesional skin. Bar length represents the log-transformed LDA score, reflecting the effect size of species abundance differences. *S. hominis* and *C. acnes* were identified as robust biomarkers of healthy and non-lesional skin, whereas *F. magna*, *C. simulans*, *P. grossensis*, *C. ureolyticus* were significantly enriched in HS lesions. Statistical significance for abundance plots was determined using Kruskal-Wallis tests for multi-group comparisons with p -values adjusted using the Benjamini-Hochberg procedure. Significance levels correspond to * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

commensals such as *S. hominis*, *S. epidermidis*, *C. acnes* and *A. octavius* showed an opposite, potentially protective trend. Notably, *Peptoniphilus* members and *F. massiliensis* also positively correlated with patient age, although not reaching significance, whereas *S. hominis* and *A. octavius* displayed an inverse trend (Figure 4a). A Random Forest Classifier identified *C. acnes*, *P. lacrimalis* and *P. grossensis* as the strongest predictors of the HS phenotype (Figure 4b), highlighting their potential diagnostic utility in HS patients monitoring (Figure 4c; AUC of 0.92).

To characterize potential microbial interactions between key taxa in the context of HS, we performed

co-occurrence and SparCC network analyses. We observed strong negative correlation between beneficial commensals (*S. epidermidis*, *S. hominis*, *C. acnes*) and HS-associated pathogens, particularly the *Peptoniphilus* species. Conversely, positive correlations among GPAC members suggest synergistic interactions within the lesional niche (Figure 4d,e). These findings were corroborated by SparCC network analysis, both for key commensals (Figure S5; *C. acnes* and *S. hominis*) and pathogens (Figure S6; *P. grossensis* and *C. ureolyticus*). These findings establish a link between clinical progression and a stable, synergistic dysbiosis that intensifies over time.

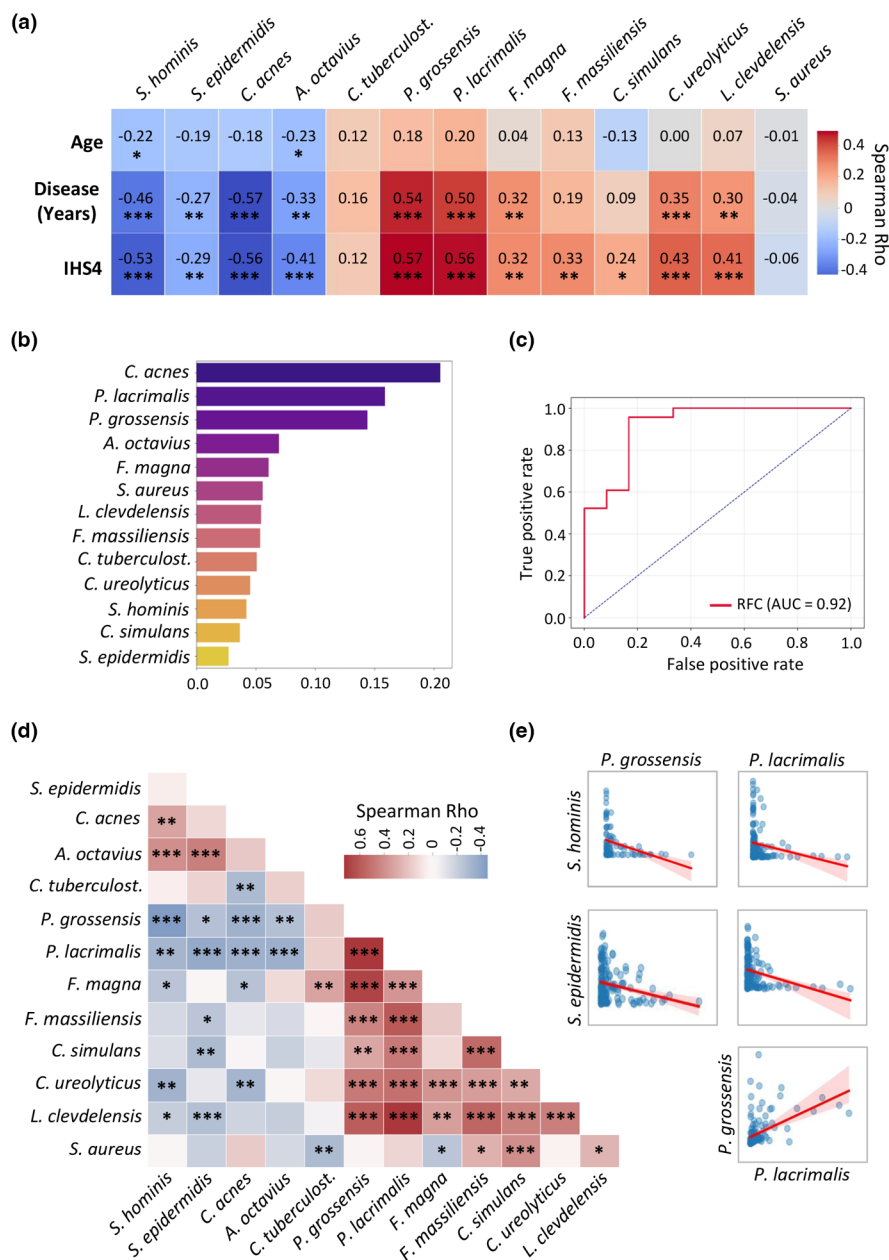


FIGURE 4 Clinical associations and predictive modelling of the HS microbiome identify signature taxa linked to disease severity. (a) Heatmap of Spearman rank correlations between the relative abundance of differentially regulated species and clinical parameters. The colour gradient represents the correlation coefficient (ρ : Rho), with red and blue indicating positive and negative associations, respectively (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). (b) Variable importance plot from a Random Forest Classifier (RFC) identifying the top 13 microbial taxa most discriminative of the HS phenotype. (c) Receiver Operating Characteristic (ROC) curves evaluating the performance of microbial markers in differentiating HS from healthy skin; the Area Under the Curve (AUC) is reported for the model. (d) Correlation matrix and (e) representative linear regression plots of specific taxa-taxa interactions. Spearman's coefficient (ρ) was used for continuous taxa-taxa and taxa-metavariable interactions, while Kruskal-Wallis and Wilcoxon-Mann-Whitney tests were applied for multi-group and pairwise abundance comparisons. Significance levels correspond to * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

Systemic antibiotic therapy moderately improves HS skin microbial dysbiosis

Next, in a sub-cohort of 28 patients, we investigated the impact of three systemic therapies: clindamycin/rifampicin (ATB), adalimumab (ADA) and secukinumab (SEC) on HS skin dysbiosis. Evaluated clinical parameters were well-balanced across the treatment cohorts, and no statistically

significant differences were observed at baseline (Table S1). At the clinical level, all three therapeutic interventions successfully mitigated disease severity over the 12-week treatment period, as evidenced by a significant reduction in longitudinal IHS4 scores from baseline (ATB, $p = 0.0038$, ADA, $p = 0.0057$ and SEC, $p = 0.02$). While all three treatments resulted in significant within-group clinical improvements, direct between-group comparisons revealed

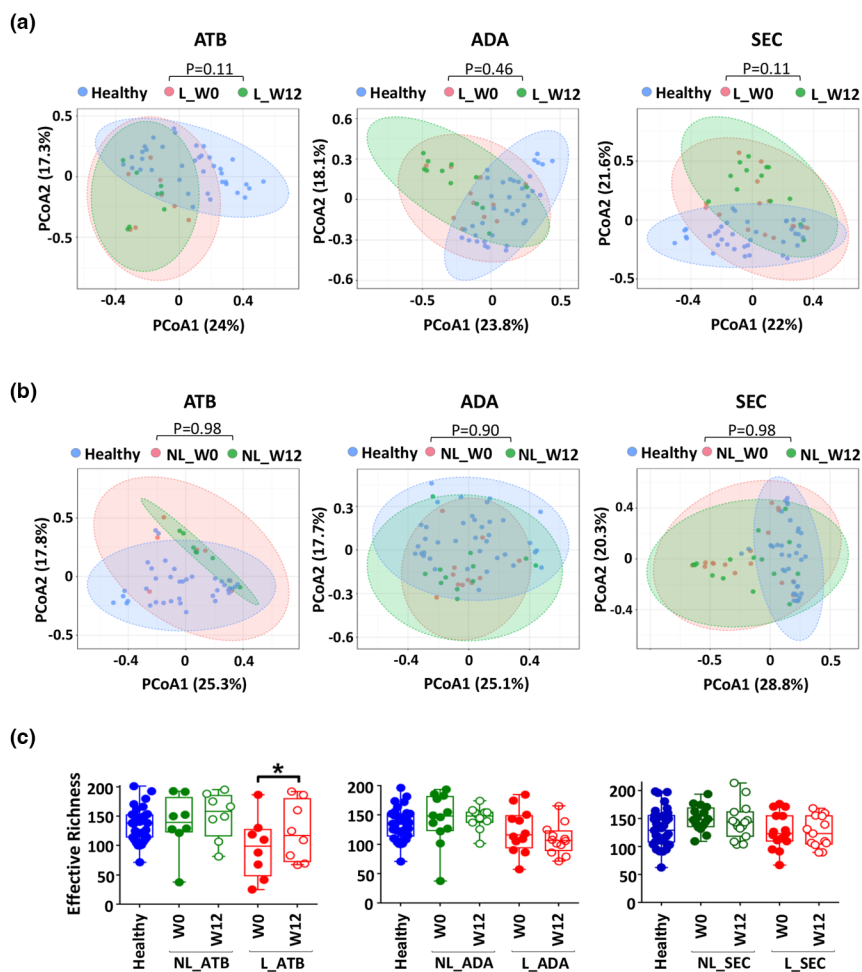


FIGURE 5 Longitudinal impact of ATB, ADA and SEC systemic therapies on HS cutaneous microbial diversity. A sub-cohort of moderate-to-severe HS patients ($n=28$) was longitudinally sampled across three 12-week treatment arms: (i) oral clindamycin/rifampicin (ATB, $n=8$); (ii) subcutaneous adalimumab (ADA, $n=12$); and (iii) subcutaneous secukinumab (SEC, $n=8$). (a) Principal Coordinates Analysis plots of β -diversity illustrating microbiome community shifts in lesional and (b) non-lesional HS skin following 12 weeks of therapy. (c) Analysis of microbial richness (Observed ASVs/Species) at baseline (Day 0) compared to Week 12 post-treatment across all cohorts. Statistical significance was determined using Wilcoxon signed-rank tests for longitudinal (paired) comparisons and Kruskal-Wallis with post-hoc Benjamini-Hochberg correction for cross-sectional group comparisons.

no significant differences in absolute Δ IHS4 or percentage IHS4 reduction. However, their capacity to modulate the underlying cutaneous dysbiosis diverged sharply. β -diversity analysis demonstrated that both ATB and SEC treatments induced a non-significant trend ($p=0.11$) towards microbial shifts in lesional skin without affecting non-lesional sites (Figure 5a,b). Importantly, ATB was the only treatment significantly increasing microbial richness in HS lesions.

Conversely, ADA treatment led to a slight decrease in richness, while SEC resulted in no significant changes (Figure 5c). Furthermore, ATB noticeably decreased the proportions of pathogens *C. ureolyticus* and *F. massiliensis*, while preserving the commensals *S. epidermidis* and *S. hominis*. It also significantly increased the abundance of the commensal *C. tuberculostrictum*. In contrast, ADA and SEC did not exert meaningful pressure on the pathogenic consortium and led to a slight decrease in *S. epidermidis* and *S. hominis* levels. Notably, none of the investigated treatments increased *C. acnes* abundance (Figure 6a–c, Figure S7a,b).

These findings suggest that systemic antibiotics exert a strong modulating influence on the cutaneous microbiota in HS, whereas biologic regimens do not appear to drive significant microbial shifts.

DISCUSSION

The observed efficacy of antibiotic therapy in HS suggests that microbial dysbiosis plays an important role in disease pathogenesis.^{15,33} Nevertheless, detailed characterization of the HS microbiome and its dynamic response to treatment has remained limited.³⁴ Our study addresses this gap through a comprehensive analysis of the HS microbiome and the first evaluation of microbial changes induced by three widely used therapies, namely clindamycin/rifampicin, adalimumab and secukinumab. 16S rRNA analysis of 251 samples from HS patients and controls confirms profound microbial dysbiosis in HS lesions, characterized by reduced diversity and

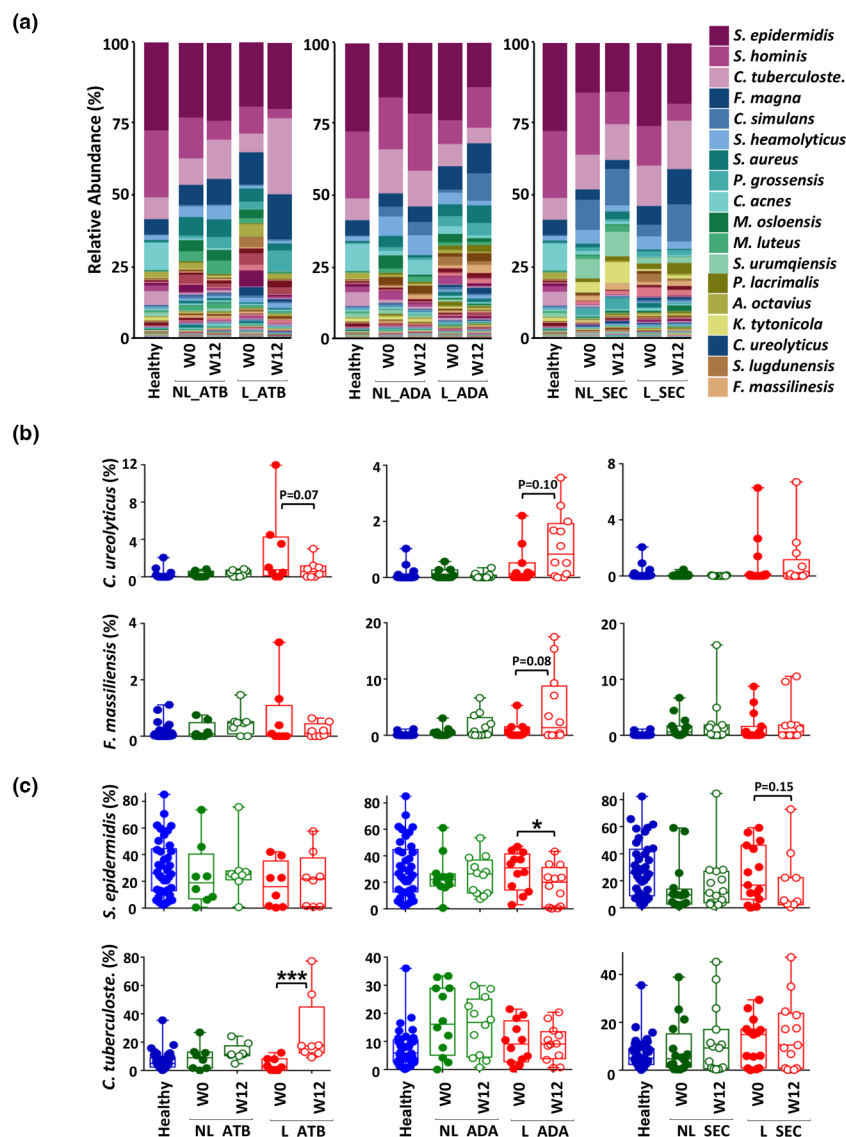


FIGURE 6 Antibiotic therapy noticeably reduces pathogen loads and restores skin commensals in HS patients. (a) Stacked bar charts illustrating the taxonomic composition at the species level across the three treatment arms at baseline (W0) and week 12 (W12). Relative abundance plots depicting changes of (b) HS-associated pathogens and (c) dominant skin commensals following 12 weeks of ATB, ADA and SEC therapies. Statistical significance was determined using Kruskal-Wallis tests for multi-group comparisons and Wilcoxon signed-rank tests for longitudinal (paired) comparisons. The asterisks indicate statistically significant differences and correspond to * $p \leq 0.05$, *** $p \leq 0.001$.

the displacement of homeostatic commensals by GPAC anaerobic pathogens. β -diversity analysis demonstrated distinct clustering of the lesional HS microbiome compared to non-lesional or healthy controls, unlike patterns observed in psoriasis and atopic dermatitis where non-lesional skin shows an intermediate microbial state.^{35,36} The reduced microbial richness in severe HS lesions aligns with previous reports implicating dysbiosis in HS pathogenesis.^{14,37} Interestingly, the non-lesional HS skin already harbours an asymptomatic dysbiosis similar to lesional sites, which may suggest a field effect that could potentially predispose normal-appearing skin to inflammation.

The expansion of a pathogenic consortium, including *Finegoldia magna*, *Peptoniphilus grossensis* and *Fenollaria*

massiliensis, corroborates previous reports of anaerobic overgrowth in HS.^{14,38} Furthermore, our findings highlight *Campylobacter ureolyticus*^{14,39} and *Lawsonella clevelandensis*⁴⁰ as potential contributors to disease severity. We also detected *S. aureus* in 37% of HS patients, consistent with its identification in severe cases.^{14,41} Intriguingly, Ring and colleagues^{15,37} reported a prominent expansion of opportunistic *Prevotella* and *Porphyromonas* species, in contrast to our findings. Conversely, HS lesions exhibited a marked depletion of beneficial commensals, including *Staphylococcus hominis*, *Cutibacterium acnes* and *Staphylococcus epidermidis*. These gatekeeper species are known to reinforce skin barrier integrity, modulate immune responses and produce antimicrobials like bacteriocins and lantibiotics.^{42–44} The

loss of these commensals is associated with compositional shifts and may facilitate opportunistic pathogenic colonization, as previously reported for *S. epidermidis*³⁹ and *Cutibacterium*.⁴⁵

The loss of site-specific microbial signatures in HS, where axillary and inguinal regions become compositionally similar, further implies that HS pathology overrides the ecological influence of local skin microenvironments, favouring a uniform, dysbiotic state. This aligns with observations by Ring and co-authors,¹⁵ reporting a high similarity between the axilla and groin microbiomes in HS. The negative correlation between key commensals and HS severity supports their protective role, consistent with findings in other inflammatory skin diseases.^{46,47} Meanwhile, the correlation between GPAC members and disease duration may indicate that long-standing HS aligns with the progressive establishment of anaerobic biofilm communities, which could offer a plausible explanation for the diminished therapeutic response in advanced Hurley stages.³ Our linear discriminant analysis and Random Forest Classifier successfully validated this signature, achieving an AUC of 0.92. The high variable importance scores for *C. acnes* and *Peptoniphilus* members suggest that microbial profiling could serve as a robust diagnostic tool for HS staging and monitoring.⁴⁸ We previously reported the expansion of *C. simulans* in the lesional skin of patients with Darier's disease, where it correlated strongly with odour intensity.⁴⁹ Consequently, the increased abundance of this taxon in HS skin may contribute to the characteristic clinical malodour as well.

The comparative analysis of systemic therapies reveals a distinct divergence in microbial modulation. ATB therapy was the only intervention that noticeably reduced pathogen burden while increasing microbial richness. This increase in diversity likely results from the suppression of dominant anaerobes, allowing for the expansion of diverse taxa, particularly *C. tuberculostrictum*, into the vacated niche. However, the failure of ATB to restore *C. acnes* levels indicates that standard antimicrobial therapy is insufficient to achieve complete ecological restoration. In contrast, ADA and SEC demonstrated negligible impacts on the microbial composition. While these agents effectively suppress TNF- α and IL-17A mediated inflammation,^{18,19} they do not rectify the observed dysbiosis and even reduce the proportions of commensals such as *S. epidermidis* and *S. hominis*. A single study recently investigated the effects of adalimumab on the facial HS skin microbiota, but did not find any differences in comparison to healthy controls, neither in microbial diversity nor in relative abundances of taxa.⁵⁰ The persistence of pathogenic anaerobes during biologic therapy may provide a rationale for the high rates of clinical relapse upon treatment cessation. Notably, blocking IL-17A via secukinumab did not further exacerbate or ameliorate the existing dysbiosis. We hypothesize that in the chronically inflamed HS environment, the IL-17-driven induction of antimicrobial peptides, such as β -defensins and cathelicidins,⁵¹ may already be decoupled

from effective microbial control. Consequently, the native antimicrobial barrier is so profoundly compromised by the underlying pathology that the impact of therapeutic IL-17A blocking on the skin's ecological landscape remains negligible.

In conclusion, our exploratory findings suggest that HS is associated with a stable, synergistic dysbiosis that correlates with clinical severity and chronicity. The displacement of protective commensals by an anaerobic consortium appears to be a central feature of the HS lesional environment. While systemic antibiotics were associated with ecological shifts, tested biologics did not noticeably alter the cutaneous microbiome, suggesting that future strategies may benefit from combining microbiome-targeted therapies with immunomodulation. Indeed, recent clinical data demonstrate that initiating adalimumab in combination with clindamycin and rifampicin significantly improves therapeutic efficacy, particularly regarding deep draining tunnels, compared to biologic monotherapy.⁵² Aligning with the European S2k guidelines,¹⁶ which advocate for multi-modal and holistic therapeutic interventions, such combination regimens likely offer a synergistic clinical benefit by simultaneously suppressing host-driven inflammation and ameliorating local microbial dysbiosis. Study limitations include a small, non-randomized longitudinal cohort subject to confounding by indication. The sampling via surface skin swabbing primarily captures the superficial stratum corneum microbiota, leaving the deep microenvironments of inflamed hair follicles and dermal tunnels underrepresented. Moreover, taxonomic profiling via 16S rRNA gene sequencing yields compositional data, reflecting proportional changes rather than absolute microbial counts. Finally, despite strict clinical inclusion/exclusion criteria, residual confounding from unmeasured lifestyle (including body mass index and smoking status), dietary or environmental factors cannot be entirely ruled out. Future validation requires prospective randomized controlled trials alongside deep-tissue sampling, absolute quantification and functional multi-omics to determine whether this dysbiosis actively drives inflammation or reflects a secondary host response.

AUTHOR CONTRIBUTIONS

Yacine Amar: Writing – original draft, conceptualization, methodology, investigation, formal analysis, data curation, supervision, funding acquisition. **Diana Baumann:** Methodology. **Sebastian Niedermeier:** Methodology. **Rafaela L. Silva:** Methodology. **Susanne Walch:** Methodology. **Michael Schlöter:** Conceptualization, writing—review and editing. **Martin Köberle:** Conceptualization, writing—review and editing. **Tilo Biedermann:** Conceptualization, writing—review and editing, supervision, funding acquisition. **Thomas Volz:** Conceptualization, methodology, writing—review and editing, supervision, funding acquisition.

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CONFLICT OF INTEREST STATEMENT

Thomas Volz received grants, consulting fees or honoraria from AbbVie, Novartis, HiPP and UCB Pharma. Tilo Biedermann received honoraria, research grants or advisory fees from AbbVie, Alk-Abelló, Almirall, Lilly, Novartis, Sanofi-Genzyme and Viatris. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

The study was reviewed and approved by the Ethics Committee of the Faculty of Medicine at the Technical University of Munich (approval n. 580/16 S).

ETHICS STATEMENT

The patients in this manuscript have given written informed consent to the publication of their case details.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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