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***CUTANEOUS MICROBIOME IN HIDRADENITIS
SUPPURATIVA***

SUMMARY OF THE DOCTORAL THESIS

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition, characterized by painful nodules[1], abscesses, fistulas, and scars [2], located predominantly in intertriginous areas [3]. Although not an infectious disease in the classical sense, the presence and activity of skin bacteria are involved in the pathogenesis and perpetuation of inflammation [4][5]. Therapeutic options range from topicals, systemic treatments with antibiotics, retinoids, or biologics [6], and wide surgical excision remains the gold standard for severe stages [7]. In the context of expanding research on the human microbiome, interest in the skin microbiota in HS has increased considerably [8]. Recent literature highlights the crucial role of the skin microbiome in the etiopathogenesis of this disease, suggesting that microbial dysbiosis may constitute a determining factor in the initiation and perpetuation of chronic inflammation [9][10]. However, the existing data are still fragmented and inconsistent, and the analysis methods vary considerably between studies. This paper analyses the composition of the skin microbiome in patients with HS, to understand the mechanisms of the disease. The thesis was motivated by the need to elucidate this relationship, with the aim of contributing to the development of personalized and effective therapeutic strategies. The novelty of the study consists in the detailed analysis of bacterial diversity and biofilm formation in HS lesions, essential aspects for understanding the mechanisms of bacterial persistence and chronic inflammation. The timeliness of the topic is emphasized by the increasing incidence of HS and the need for more effective and personalized treatments, as well as the need for further research to clarify these aspects [11]. The hypothesis we started from is that the skin microbiome of patients with HS is significantly altered, both in terms of bacterial composition and associated metabolic functions, and that these differences contribute to the establishment and maintenance of the inflammatory process characteristic of the disease. Furthermore, we assume that certain microbial changes may constitute predictive biomarkers or viable therapeutic targets for a personalized treatment approach. The proposed research hypothesis is that bacterial diversity and biofilm formation in HS lesions are correlated with disease severity, treatment response, and periods of exacerbation. It is assumed that certain bacterial species, such as *Staphylococcus aureus* and *Corynebacterium spp.* play a crucial role in the pathogenesis of HS by producing virulence and antibiotic resistance factors.

To test this hypothesis, the scientific objectives of the research were as follows:

- Characterization of the cutaneous microbiological profile in patients with HS;
- Identification and characterization of bacterial strains isolated from HS lesions;
- Evaluation of microbial diversity in relation to disease severity;

- Identification of significant differences in microbiome composition between groups;
- Study of biofilm formation by isolated bacterial strains;
- Analysis of soluble virulence factors;
- Genotypic evaluation of virulence and resistance genes of *Staphylococcus aureus* strains by PCR;
- Evaluation of the relationship between clinical severity of the disease and microbiome particularities;
- Analysis of possible correlations between dysbiosis and local inflammatory response;

Inclusion criteria	YES	NO
Female or male patients aged between 18 and 70 years	☐	☐
The subject must have had HS skin lesions for at least 1 year	☐	☐
To have at least one anatomical region with inflammatory (active) lesions	☐	☐
The patient has a good general condition according to the physical examination and medical history	☐	☐

Exclusion criteria	YES	NO
The patient has any other active disease (e.g., infections) that may interfere with the result of bacteriological research	☐	☐
The subject has administered topical treatments (except antiseptics) 30 days before the collection of bacteriological samples	☐	☐
The subject received systemic antibiotic treatment 1 month before the collection of bacteriological samples	☐	☐

The methodology used was integrative, involving the collection of samples from HS lesions, cultivation of bacteria, identification and characterization of these by microbiological and molecular methods. The method includes both rigorous clinical evaluations of patients and standardized collection of skin samples from affected and unaffected areas, followed by advanced microbiological analysis. All patients included in the study underwent bacteriological examination from two depth sites. One superficial - swab, the other deep, by punch biopsy. The bacteriological examination was performed in aerobic and anaerobic environment. Two types of bacteriological samples were collected. Collection on a sterile swab was done from superficial purulent lesions, without prior cutaneous asepsis, with rapid transport medium for inoculations on culture media. Non-suppurative, closed lesions were accessed by two punch biopsies preceded by cutaneous asepsis with 10% povidone-iodine solution. One specimen was

placed in a sterile container, and the other in a gas tube without oxygen. The lesions that cause the most discomfort for each patient in terms of inflammation, pain, recurrence and suppuration were selected. The samples were sent to the laboratory within a maximum of one hour after collection.

Aerobic and anaerobic bacterial cultures were performed, strain identification by classical and automated methods (VITEK, MALDI-TOF), antibiotic susceptibility tests, and biofilm evaluation by colorimetric methods using microtiter plates. The analysis of virulence factors addresses the production of soluble virulence factors (hemolysins, lipases, lecithinases, DNA-ases), demonstrating the heterogeneity of bacterial aggressiveness depending on species and isolate, and some of the strains were analyzed by molecular biology techniques (PCR) for the identification of virulence and antibiotic resistance genes.

A comprehensive statistical analysis was performed to assess the association between Hurley stage of HS and various isolated bacterial species. Statistical calculations were performed using IBM® SPSS® version 30.0.0 software. The analysis included both parametric and non-parametric tests to ensure robustness and accuracy. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the "Elias" University Emergency Hospital, Bucharest (no. 4490/23.06.2021). Participants provided written informed consent to participate in this study.

The research undertaken within this thesis brings a series of original contributions, which can be classified according to their scientific and applicative nature.

1. Development of a standardized protocol for the collection and processing of skin samples

A reproducible and efficient protocol was developed for the collection, preservation and processing of skin samples for bacterial analysis, adapted to the infrastructure in Romania. It can also be adopted by other research and dermatology centres.

2. Participation in the drafting and publication of specialized scientific articles

The research results were disseminated in the scientific community through participation in international conferences and the publication of an article in a Web of Science, ISI indexed journal (see the list of published scientific papers). This consolidates the validity and impact of the contributions.

3. Creation of a microbial database specific to patients with HS

For the first time in the Romanian specialized literature, a detailed microbiological database of patients with HS was constructed, including microbial diversity profiles for several anatomical regions. This database constitutes a valuable benchmark for future research in dermatology and microbiology.

4. Identification of dysbiosis in HS (Chapter 6. Study I)

One of the major contributions of the research was the isolation and identification of bacterial strains from HS lesions, using advanced microbiological and molecular methods. The first study is an observational, prospective one, based on bacterial cultures, conducted on a group of 40 patients diagnosed with HS. The main objective of the study was to isolate and identify the bacterial strains present in the superficial and deep lesions of patients with HS, as well as to evaluate the correlations between bacterial diversity, disease severity and certain host factors. This allowed obtaining a detailed picture of bacterial diversity and the prevalence of different bacterial species in HS lesions. Secondary objectives include the evaluation of differences in bacterial diversity according to clinical severity (Hurley I–III), establishing the correlation between bacterial density and lesion location, identification of antibiotic-resistant strains, and evaluation of the distribution of aerobic vs. anaerobic species and the mono/polymicrobial character of the colonies. Bacteriological samples were collected by superficial swabbing and deep punch biopsies, and the samples were cultured in both aerobic and anaerobic media. The identification of bacteria was performed by classical and automated methods.

A total of 201 bacterial strains were isolated, highlighting a polymicrobial flora in most cases. The most common strains in superficial lesions were: *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Staphylococcus lugdunensis*, *Peptoniphilus spp.*, *Enterococcus faecalis*. In deep lesions, the predominant ones were: *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Corynebacterium tuberculostrictum* [12]. A greater bacterial diversity was noted in male patients and in those with severe forms of the disease (Hurley III). The proportion of multidrug-resistant bacterial strains was lower than that reported in the international literature, totalling only 8.95% of the isolates.

The results support the existence of a specific cutaneous dysbiosis in HS, characterized by a decrease in normal bacterial biodiversity, colonization with anaerobic species and

pathogenically modified commensal species. These changes are more pronounced in chronic lesions, deep lesions, severe clinical cases. The data obtained suggest that therapeutic intervention should be adapted to the individual microbiological profile and that a personalized approach could improve the prognosis [12].

5. Study of Biofilm Formation (Chapter 7. Study II)

The research investigates the ability of the isolated strains to form biofilm, an essential mechanism in the persistence of inflammation and therapeutic resistance. The strains from chronic lesions showed significantly higher biofilm activity. The central hypothesis of the study was the idea that bacterial strains isolated from HS lesions have a different ability to form biofilm, which can influence the persistence of infection and the clinical severity of the disease. The aim was to evaluate this capacity, correlated with the phenotypic and genotypic profile of virulence, especially for *Staphylococcus aureus* strains, given their frequency in HS and the potential for multiple antibiotic resistance. 23 patients with chronic HS, hospitalized at the "Elias" University Emergency Hospital in Bucharest, were included. From their lesions, 92 bacterial strains belonging to 20 species, collected from different affected regions (axillary, gluteal, inguinal, abdominal, nuchal), were isolated. Biofilm formation testing was performed in vitro by the colorimetric method with crystal violet, measuring the absorbance at 24, 48 and 72 hours. Statistical evaluation was performed using the Kruskal-Wallis test. The results showed a significant variability in the ability to form biofilm between different species.

At 24 hours, *Corynebacterium striatum* showed the highest biofilm biomass (1.02 nm), followed by *Enterococcus faecalis* and *Micrococcus luteus* [13]. At 48 hours, *Corynebacterium striatum* maintained its dominant position (1.43 nm), while other species, such as *Corynebacterium simulans* and *Enterococcus faecalis*, showed significant increases in biofilm. At 72 hours, most species recorded a decrease in biomass, but *Corynebacterium striatum* remained at the top (0.66 nm), suggesting biofilm maturation and possible partial detachment. Species such as *Brevibacterium celere* and *Acinetobacter nosocomialis* continued biofilm development, suggesting a slower formation rate. Statistical analysis confirmed significant differences between bacterial species in all three-time intervals, with p values below 0.01. These results highlight the heterogeneous nature of biofilm formation and the potential impact on bacterial persistence in HS lesions. The results demonstrate that bacterial biofilms contribute to increased tolerance to antibiotics and evasion of the host's immune response. Strains with a high capacity to form biofilm, such as *Corynebacterium striatum*, could play a central role in

the chronicity of the disease. This phenomenon partially explains why HS infections are recalcitrant to standard treatments. In addition to biofilm formation, an association between increased virulence and infection persistence was also observed. The limitations include the small sample size and the exclusive use of in vitro tests for biofilm evaluation, which cannot completely reproduce the biological conditions in real lesions. Future studies are recommended to use in vivo models and advanced metagenomic methods to obtain a complete picture of microbial biofilm in HS.

6. Analysis of Soluble Virulence Factors (Chapter 8. Study III)

The main purpose of this study was to phenotypically analyse the production of soluble virulence factors of bacterial strains isolated from the lesions of patients with HS. The study investigated eight enzymatic factors (hemolysins, lecithinase, lipase) and exoenzymes (caseinase, gelatinase, amylase, DN-ase and esculinase), which contribute to the aggressiveness of pathogens and tissue damage. Bacterial strains were cultured on special media, supplemented with enzymatic substrates, and evaluated at 24 and 72 hours. The expression of each factor was assessed based on visual changes in the medium (e.g., zones of hemolysis or precipitation). A semi-quantitative scale (0–3) was used for the intensity of the enzymatic response. *Staphylococcus spp.* expressed hemolysins intensely (94.64% of strains), lecithinase (62.5%) and lipase (41%).

These enzymes are associated with bacterial invasiveness and dissemination, as well as with iron mobilization, which activates the expression of other virulence genes. *Corynebacterium spp.* showed a similar, but less intense, enzymatic profile: hemolysins (75%), caseinase (37.5%), lecithinase (31.25%) and lipase (18.75%). Gelatinase and DN-ase were not detected. *Enterococcus spp.* expressed esculinase (90%), caseinase (60%) and lipase (50%), without hemolytic or lecithinase activity. Gelatinase and DN-ase were not detected in any species tested, suggesting a minor role in the virulence of the strains involved in HS. The virulence index calculated by summing the scores highlighted a clear superiority of *Staphylococcus spp.* compared to the other bacterial genera, which indicates a greater pathogenic potential and a central role in the chronicity of the infection [13]. In conclusion, the enzymatic profiles of bacterial strains reveal different mechanisms of tissue aggression depending on the genus and species analysed. This diversity can influence disease severity, treatment response and the potential for chronicity. The study proposes the integration of phenotypic virulence testing into diagnostic and therapeutic strategies, in order to individualize

the management of the patient with HS. The results offer promising perspectives for the development of targeted therapies – for example, enzyme inhibitors – and for clinical risk stratification based on the individual bacterial profile. This study reinforces the idea that not only the presence of bacteria, but also their functional behaviour (active virulence) is essential in the pathogenesis of HS.

7. Genotypic Evaluation of Virulence and Resistance Genes of *Staphylococcus aureus* Strains by PCR (Chapter 8. Study IV)

The purpose of this study was to investigate the genotypic virulence and antibiotic resistance profiles of *Staphylococcus aureus* strains isolated from patients with HS, using Polymerase Chain Reaction (PCR) techniques. The aim was to correlate these profiles with disease severity and potential clinical implications. 35 *Staphylococcus aureus* strains were analysed for virulence genes and 12 strains for resistance genes. The PCR technique was applied using simplex and multiplex reactions for 20 relevant target genes. PCR products were visualized by agarose gel electrophoresis and compared with molecular markers for validation. The investigated genes were:

- Virulence: *clfA*, *clfB*, *fnbA*, *fnbB*, *fib*, *bbp*, *ebpS*, *cna*, *tst*, *sea*, *seb*, *sec*, *sed*, *see*, *luk-PV*, *hlg*, *coa*.
- Resistance: *mecA*, *ermA*, *ermC*, *nuc*, *SCCmec*, recombinase genes (*ccrB2*, *ccrC*, *CIF2*), and others involved in chromosomal cassette mobility and ionic homeostasis (*kdp*).

Genes such as *clfA*, *fnbA*, *fib*, and *mecA*, which play a crucial role in HS pathogenesis and antibiotic resistance, were identified.

Virulence Genes

The *clfA* gene was detected in 97.14% of strains, indicating an increased capacity for bacterial adhesion. The *fnbA* gene was present in over 88% of isolates, strengthening the hypothesis of fibronectin adhesion involvement in HS pathogenesis. Other frequently detected genes included *fib* (fibrinogen binding), *hlg* (gamma hemolysin), and *coa* (coagulase). Toxin genes such as *tst* (toxic shock syndrome toxin) and *sec/sed* were rarely positive (2.85–8.57%); *sea*, *seb*, *see*, and *luk-PV* were absent.

Resistance Genes

MecA (encoding PBP2a, associated with MRSA) was identified in 50% of the tested strains, confirming a high rate of beta-lactam resistance. The *ermC* gene, responsible for macrolide resistance, was present in 25% of isolates; *ermA* was absent. The *ccrB2* and *CIF2* genes, involved in *SCCmec* mobility, were detected in 41.66% of cases, but *ccrC* was absent[13].

The massive presence of genes involved in adhesion and invasiveness suggests an essential role for *Staphylococcus aureus* in the chronicity and aggressiveness of HS lesions. The high MRSA rate highlights the need to re-evaluate treatment strategies, including systematic molecular testing of strains from lesions. The absence of the *luk-PV* gene suggests a different pathogenicity compared to classic virulent community strains, with a lower potential for inducing necrotizing lesions. The genotypic virulence profile of *Staphylococcus aureus* strains in HS indicates an increased capacity for adhesion and colonization but a limited expression of toxic genes. The genotypic resistance profile signals a high prevalence of MRSA strains, justifying the inclusion of genetic tests in the clinical management of HS. These data support innovative therapeutic approaches focused on inhibiting bacterial adhesion and controlling antimicrobial resistance.

The thesis validates the hypothesis of a pathogenic dysbiosis in HS, with significant alteration of the skin microbiome, active involvement of virulent and biofilm-producing bacteria, and limitation of standard antibiotic therapy efficacy. These data support the need for rethinking the therapeutic approach, with an emphasis on microbiome-targeted therapies and biofilm control. The author directly contributed to all stages of the study: experimental design conception, sample collection and processing, interpretation of microbiological data, development of clinical and statistical correlations, writing, and dissemination of results. The work integrates clinical dermatology, microbiology, immunopathology, and molecular biology. The applicability of the results extends to other inflammatory dermatoses, opening research directions such as the use of prebiotics, testing of anti-biofilm molecules, and personalization of antibiotic therapy based on individual microbiome profiles.

The main objective of this doctoral thesis was to investigate the skin microbiome in patients with hidradenitis suppurativa. The research objectives were largely achieved, providing a detailed understanding of bacterial diversity and biofilm formation in HS lesions. The study successfully isolated and identified bacterial strains from HS lesions and characterized

virulence factors. It also demonstrated the correlation between bacterial diversity and biofilm formation. The research showed that the skin microbiome of HS patients is significantly altered, being dominated by certain pro-inflammatory bacterial species (e.g., *Corynebacterium*, *Staphylococcus aureus*, *Porphyromonas*, *Peptoniphilus*, *Anaerococcus*, and *Prevotella*), and a decrease in commensal genera (e.g., *Cutibacterium*, *Staphylococcus epidermidis*). These changes were correlated with the disease stage.

The technical and economic advantages of the research include the use of advanced microbiological and molecular methods for identifying and characterizing bacterial strains, which allowed for precise and relevant results. The study also contributed to the development of personalized therapeutic strategies that can reduce long-term treatment costs by improving their effectiveness. Technical and economic disadvantages include the high costs associated with advanced analytical techniques, the need for advanced bioinformatics infrastructure, and the need for specialized equipment. Additionally, the small sample size may limit the generalization of results, necessitating further studies on larger cohorts.

Although the work makes significant contributions to understanding microbial changes in HS, there are several unresolved aspects that can constitute future research directions:

- Individual variability of patients and the complexity of interactions between different bacterial species in HS lesions.
- Causality of microbiome changes: it is not clear whether dysbiosis is the cause or effect of chronic inflammation in HS.
- The study failed to identify all mechanisms by which biofilm contributes to the chronicity and antibiotic resistance of HS lesions.
- The impact of systemic treatments on the microbiome remains partially understood, especially in the case of biological therapies.
- The role of the non-bacterial microbiome (fungal and viral), which was not addressed in this work, but could be relevant in HS.

Based on current conclusions, future research should focus on advanced longitudinal studies to analyse bacterial diversity at the species and genus level, extending metagenomic analysis to the non-bacterial microbiome. It would be relevant to evaluate how the microbiome changes over time and responds to treatments (surgical, biological, antibiotics). It is also important to investigate the interactions between the skin microbiome and the host immune

system (investigating the microbiome-immune system-skin axis, with an emphasis on molecular mechanisms), as well as the impact of environmental factors and lifestyle on the skin microbiome. Longitudinal studies investigating the dynamics of the skin microbiome in relation to the clinical evolution and treatment of HS, with investigation of the therapeutic potential of microbiome manipulation (interventional studies with probiotic administration or skin microbiome transplant) and the development of anti-biofilm agents and personalized antibiotic regimens, represent other important research directions.

The research highlighted the importance of biofilm and virulence factors in the chronicity and treatment resistance of HS lesions. These findings have significant clinical implications, suggesting the need to develop targeted therapies that aim at biofilm and virulence factors. The study also emphasizes the importance of personalizing treatment based on the skin microbiome profile of each patient.

The limitations of the research include the small sample size and individual patient variability. To validate these findings, studies on larger cohorts and the use of advanced metagenomic analysis techniques are needed. Future research perspectives include the development of anti-biofilm agents and personalized antibiotic regimens, based on the skin microbiome profile of each patient. Continued research could involve multicentre studies, correlation with host gene expression, creation of clinical protocols for microbial restoration, and exploration of the effect of probiotic interventions in HS.

In conclusion, the research successfully achieved its proposed objectives, providing a detailed understanding of bacterial diversity and biofilm formation in HS lesions. The study highlighted the importance of virulence factors and antibiotic resistance in HS pathogenesis, suggesting the need for personalized therapeutic strategies. The research also opened new perspectives for future studies, emphasizing the importance of an interdisciplinary approach to understanding and treating HS.

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List of published scientific papers

1. **Phenotypic and Genotypic Bacterial Virulence and Resistance Profiles in Hidradenitis Suppurativa** International Journal of Molecular Sciences, 26(8), 3502. **Cucu, C. I.**, Giurcăneanu, C., Poenaru, E., Popa, L. G., Popa, M. I., Chifiriuc, M. C., Lazăr, V., Holban, A. M., Gheorghe-Barbu, I., Muntean, A.-A., Caracoti, C. Ș., & Mihai, M. M. (2025). ISI IF 5,6 <https://doi.org/10.3390/ijms26083502> (Capitol 7, Studiul II, Capitol 8, Studiul III, Capitol 9, Studiul IV)
2. **Unraveling the Skin Microbiome in Hidradenitis Suppurativa: Implications for Treatment and Disease Progression** Journal of Clinical Medicine, 14(7), 2424. **Cucu, C. I.**, Giurcăneanu, C., Mihai, M. M., Andronic, T., Ancuta, I., Popa, M. I., Macovei, I. S., & Popa, L. G. (2025) ISI IF 3 <https://doi.org/10.3390/jcm14072424> (Capitol 6, Studiul I)
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8. **A Complementary Therapeutic Option for the Management of Hidradenitis Suppurativa Based on Natural Compounds** to Frontiers in Immunology, section Systems Immunology. Valentina Alexandra Bădăluță, Adrian Ionascu, Lia-Mara Ditu, Curutiu Carmen, Alina Maria Holban, Eliza Oprea, Yiannis Kourkoutas, Mara Madalina Mihai, **Corina Ioana Cucu**, Ariana Hudita, Florica Marinescu and Veronica Lazar **ISI IF 5,1 - in progress of publication**

Oral presentations related to doctoral studies

1. Ultrasonographic characterization of hidradenitis suppurativa lesions, **Cucu C.I.**, Popescu M., Beiu C., Mihai M., Anghel T., Dragomir I., Giurcăneanu C., Popa L. - 21 National Dermatology Congress, Poiana Brașov, 15-18 June 2022
2. Anaerobic and microaerophilic bacteria isolated in chronic skin pathologies. Retrospective study - Macovei I.S., Mihai M.M., **Cucu C.I.**, Muntean A.A., Preda M., Dragomirescu C., Popa M.I. - The annual symposium of scientific communications of the National Institute for Medical-Military Research-Development "Cantacuzino"
3. Access of patients with suppurative hidradenitis to treatment and medical services in the current pandemic context, **Cucu C.I.**, Popa L., Mihai M., Giurcăneanu C., Orzan O. - 19 National Dermatology Congress, 14-18 October 2020
4. An update on the pathogenesis of hidradenitis suppurativa - **Cucu C.I.**, Giurcăneanu C., Popa L., National Conference of Resident Doctors, 9-11 June 2021

Poster presentations related to doctoral studies

1. How diverse is the microbiome of hidradenitis suppurativa? Case series - **Cucu C.I.**, Mihai M.M., Popa L.G., Macovei I.S., Popa M.I., Muntean A., Dragomirescu C., Giurcăneanu C., EADV Symposium Innovation blossoms in dermatology-venereology, Ljubljana - 12-14 May 2022
2. Rare onset of hidradenitis suppurativa 11 years after menopause, **Cucu C.I.**, Miulescu R., Popa L., Mihai M., Orzan O. - Conference of the European Hidradenitis Suppurativa Foundation, Athens - February 2020, abstract published in Special Issue Experimental Dermatology 21 July 2020 Volume29, IssueS1 <https://doi.org/10.1111/exd.14122>