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REVIEW

The Microbiome in Hidradenitis Suppurativa: A Review

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ABSTRACT

Introduction: Hidradenitis suppurativa (HS) is a chronic autoinflammatory skin disease. It is characterised by the development of abscesses and nodules in intertriginous anatomical sites. Whilst it is now recognised as an autoinflammatory condition rather than an infective disease, bacteria are implicated in disease pathogenesis.

Methods: We performed a search of the literature from inception to 12 August 2020 using the search terms "hidradenitis suppurativa", "Verneuil's disease", "acne inversa", "microbiome", "bacteriology" and "microbiology". Studies were included if they assessed the cutaneous, gut or oral bacteria, bacteriology or microbiome in hidradenitis suppurativa.

Results: Twenty-one studies examining the cutaneous microbiome and two studies examining the gastrointestinal microbiome in HS were identified. No studies examining the oral microbiome in HS were identified. A total of 972 patients and 46 healthy controls were included across studies examining the cutaneous microbiome. A total of 100 patients and 36 controls were included across both gut microbiome studies. Coagulase-negative *Staphylococcus*, anaerobes such as *Porphyromonas* and *Prevotella*, and *Staphylococcus aureus* species were commonly encountered organisms across the included cutaneous microbiome studies. The studies examining the gut microbiome were limited, with one small study demonstrating an alteration in the gut microbiome composition compared to controls. The other study found no alteration to the gut microbiome in patients with HS compared to those with inflammatory bowel disease (IBD) and HS, and IBD and/or psoriasis.

Conclusion: Research should be undertaken into the oral microbiome in HS. Further research should be undertaken examining the cutaneous and gut microbiome in HS, and its relationship with documented co-morbidities. Additionally, metagenomics-focused studies may help identify the relationship between microorganisms and host, and this may shed light on new pathways of disease pathogenesis. This may help identify potential future therapeutic targets.

Keywords: Bacteria; Hidradenitis suppurativa; Infections; Gastrointestinal microbiome; Microbiota

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Key Summary Points

Hidradenitis suppurativa is a chronic autoinflammatory skin disease characterised by the development of abscesses and nodules in intertriginous sites such as the axilla and groin.

Anaerobic bacteria, such as *Prevotella* and *Porphyromonas*, coagulase-negative *Staphylococcus*, and *Staphylococcus aureus* were commonly identified microorganisms in HS lesions. Studies used culture, 16S RNA or a combination of these two modalities to identify which organisms were present.

There is limited research examining the gut microbiome in HS. One very small study found an alteration in the gut microbiome in patients with HS compared to healthy controls, and the other study found no difference in the HS group compared to those in the psoriasis, IBD, psoriasis and IBD, and HS and IBD groups.

There were no studies identified which examined the oral microbiome in HS.

Further research is required to help us understand how the microbiome and alterations in its composition contribute to disease pathogenesis in HS. This may help identify potential future therapeutic targets.

DIGITAL FEATURES

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic autoinflammatory skin condition characterised by recurrent abscesses and nodules in intertriginous anatomical sites, such as the axilla, groin and gluteal areas [1, 2]. There is associated purulent and malodour discharge from these lesions in many patients, and it may be initially mistaken for an infective process [3]. There is often a significant delay between disease onset and diagnosis, and many cases are only first identified in the moderate to severe stage [4]. The disease has a number of disease and lifestyle associations, including metabolic syndrome, diabetes mellitus, obesity, polycystic ovarian syndrome and smoking [5–10].

The aetiology of HS is multifactorial. Contributing factors include genetics, environmental and lifestyle factors such as cigarette smoking, bacteria and hormonal influences [3, 11, 12]. It is characterised by follicular occlusion, which has classically been considered an initiating event. In this model of HS pathogenesis, follicular occlusion and epidermal cyst formation lead to follicular rupture, and secondary bacterial infection [11].

The cutaneous microbiome consists of a diverse variety of bacteria, fungi and viruses which inhabit human skin. Across and within individuals it is taxonomically varied, and variations are dependent upon anatomical site, host and environmental factors, and the type and abundance of associated adnexal structures such as apocrine, eccrine and sebaceous glands, and hair follicles [13]. This cutaneous microbiome extends as far down as the superficial subcutaneous tissue [14]. It exists in homeostasis with the host immune system, and may provide a mutually beneficial relationship: it is involved in regulatory cytokine production, the maintenance of the epidermal barrier, keratinocyte differentiation and homeostasis, inhibition of pathogen growth, induction of local regulatory T cells and enhancement of innate immunity [15, 16]. Alterations in the composition in the microbiome, usually as a result of host and environmental factors, can shift it towards dysbiosis—a maladaptive state

which may cause or contribute towards disease pathogenesis [17].

Gut microbiome dysbiosis has been implicated in a number of diseases, including inflammatory bowel disease (IBD), atherosclerosis, autism and asthma [18]. Intestinal bacteria play an important physiological role, and are involved in immunological signalling, host cell proliferation, intestinal endocrine functions, biosynthesis of hormones, vitamins and neurotransmitters, and dietary and drug metabolism, among others [18].

Alterations to the oral microbiome can result in periodontitis, in which there is an increase in anaerobic bacteria in the oral cavity and corresponding increase in local inflammatory mediators such as tumour necrosis factor alpha (TNFα), interleukins (IL)-1, 2 and 8, and prostaglandins [19].

The role of the microbiome in HS remains an area under ongoing investigation. The use of antimicrobial agents in HS is a well-established treatment, despite HS now being recognised as an autoinflammatory rather than infective disease [20]. The microbiome has been implicated in the pathogenesis of HS, although the interaction between organisms and host remains to be fully elucidated.

METHODS

The purpose of this narrative review was to collate and review the available evidence examining the cutaneous, gastrointestinal and oral microbiome in hidradenitis suppurativa.

We searched Medline, PubMed, Google Scholar and Embase between for the period between 12 April and 12 August 2020 using the search terms “hidradenitis suppurativa”, “Verneuil’s disease”, “acne inversa”, “microbiome”, “bacteriology” and “microbiology”. Studies were included if they assessed the cutaneous, gut or oral bacteria, bacteriology or microbiome in hidradenitis suppurativa.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

We have constructed tables (Tables 1, 2, 3) which include the main findings from each included study.

RESULTS

Twenty-one studies examining the cutaneous microbiome and two studies examining the gastrointestinal microbiome in HS were identified. A total of 972 patients and 46 healthy controls were included across studies examining the cutaneous microbiome. A total of 100 patients and 36 controls were included across both gut microbiome studies.

The Cutaneous Microbiome in Hidradenitis Suppurativa

See Tables 1 and 2.

The Gastrointestinal Microbiome

See Table 3.

The Oral Microbiome

No studies were identified which examined the oral microbiome in HS.

DISCUSSION

The Main Findings

In the studies which utilised bacterial culture in their study design, *Staphylococcus aureus*, coagulase-negative *Staphylococcus* and Enterobacteriaceae species were commonly cultured [27–29, 32, 33]. In the studies utilising 16S and 18S to examine the cutaneous microbiome, *Porphyromonas* and *Prevotella* had increased abundance [21, 23, 24]. *Porphyromonas*, *Prevotella* and *Corynebacterium* were the most commonly encountered bacteria in HS tunnels [23]. Thomas et al. found that in patients with recalcitrant HS *Corynebacterium*, *S. epidermidis*, *S. aureus* and *Prevotella* were the most frequent organisms [31]. One study utilised

Table 1 Cutaneous microbiome in HS: next-generation studies (NGS) and immunofluoresence (IF) and fluorescence in situ hybridisation (FSH)

Study	Participants and methods	Anatomical location	Most common bacteria and other main findings
Riverain-Gillet et al. (2020) [21]	60 patients and 17 controls Swabs and 16S ribosomal RNA (rRNA) gene amplicon sequencing	Axilla, inguinal folds and gluteal cleft	Increased anaerobes (such as *Prevotella*), *Actinomyces*, *Campylobacter ureolyticus* and *Mobilinucus* Reduced commensals including *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Cutibacterium acnes* and other coagulase-negative staphylococci
Naik et al. (2019) [22]	12 patients and 5 controls Swabs and 16S	Axilla, gluteal crease, inguinal crease and inframammary fold	Increased gram-negative and gram-positive anaerobes. Reduced *Cutibacterium* Microbiome in Hurley stage I disease similar to healthy controls
Ring et al. (2019) [23]	32 patients Swabs of HS tunnels during deroofing and 16S	Axilla and groin	*Porphyromonas*, *Prevotella* and *Corynebacterium*
Guet-Revillet et al. (2017) [24]	65 patients Swabs, aspirates and biopsies for affected areas. Swabs for unaffected areas. Cultures and 454 high-throughput sequencing	Axilla, inguinal fold, gluteal fold, buttocks, thighs and breast	*Prevotella* and *Porphyromonas*. Increased anaerobes and reduced aerobes. *Fusobacterium* and *Parvimonas* predominated in Hurley stage III lesions
Ring et al. (2017) [25]	30 patients and 24 controls Biopsies of affected and unaffected areas. 16 and 18S	Groin and axilla. All biopsies included a hair follicle	Increased *Corynebacterium*, *Porphyromonas* and *Peptoniphilus*. Reduced *Propionibacterium*
Guet-Revillet et al. (2014) [26]	82 patients Metagenomics and culture	Inguinal fold, perineal, buttocks, thigh, gluteal fold, axilla, breast, trunk and neck	Stage I lesions: *Staphylococcus lugdensis*. Stage II–III lesions: mixed anaerobes, anaerobic actinomycetes and streptococci of the milleri group
Jahns et al. (2014) [2]	27 patients IF and FSH hybridisation on retrospective histological samples	Arm, axilla, buttocks, genitals and other	63% had bacterial colonisation. 4′,6-diamidino-2-phenylindole-positive cocci were seen in 71% of samples with biofilms and/or microcolonies. Two cases of *Propionibacterium acnes*-associated biofilms

Table 2 Cutaneous microbiome and HS: traditional culture method studies

Study	Participants and methods	Methods	Most common bacteria and other main findings
Benzecry et al. (2018) [27]	46 patients Swabs	Axilla, inframammary folds, pubis, genital, groin, intergluteal fold, buttocks and perineum	Enterobacteriaceae, *Streptococcus*, *Corynebacterium* and *Staphylococcus*
Bettoli et al. (2018) [28]	137 patients Swabs	Axilla, groin and perianal region	*Proteus*, *E. coli*, *S. epidermidis*, *Streptococcus agalactiae* and *Staphylococcus haemolyticus*
Jamalpour, Saki and Nozari (2018) [29]	26 patients Swabs	Axilla, groin, scalp, neck, buttock, back, intermammary and perineal region	*Staphylococcus aureus*, diptheroids and *E. coli*
Nikolakis et al. (2017) [30]	50 patients Swabs	Axilla, mammary, inguino-femoral, buttock, perianal and other	In stage I, *S. aureus*, obligate anaerobic gram-negative rods and enterococci. In stage II, Enterobacteriaceae, obligate gram-negative rods and coagulase-negative staphylococci. In stage III disease, obligate anaerobic gram-negative rods, Enterobacteriaceae, streptococci and *S. aureus*
Thomas et al. (2016) [31]	76 patients with recalcitrant HS Collection methodology not specified	Axilla, groin, perineum, gluteal, perianal, abdomen, thigh, mons pubis, labia, vulva, breast, inframammary fold, neck, chest, scrotum, face and occiput	*Corynebacterium* species, *S. epidermidis*, *S. aureus* and *Prevotella*
Hessam et al. (2016) [32]	113 patients Swabs	Axilla, groin, gluteal and perineum	Coagulase-negative staphylococcus, *S. aureus*, *Proteus mirabilis* and *E. coli*
Katoulis et al. (2015) [33]	22 patients Percutaneous needle aspiration	Axilla, breast, perianal, groin, rectum, buttocks and scalp	*Staphylococcus* and *P. mirabilis*
Matusiak, Bieniek and Szepietowski (2014) [34]	69 patients Swabs	Axilla and perineum	*S. epidermidis*, *P. mirabilis*, *S. aureus* and *Enterococcus faecalis*
Sartorius et al. (2012) [35]	10 patients Biopsies and agar gel cultures from deeper layers post CO_2 laser ablation	Axilla and groin	Coagulase-negative staphylococcus, anaerobic gram-positive cocci and *Corynebacterium* species

Table 2 continued

Study	Participants and methods	Methods	Most common bacteria and other main findings
Lapins, Jarstrand and Emtestam (1999) [36]	25 patients Biopsies and swabs from deeper layers post CO_2 laser ablation	Axilla and perineal region	Coagulase-negative staphylococci, *S. aureus* and *Peptostreptococcus*. *Peptostreptococcus*, *P. acnes*, *Lactobacillus* species, *Prevotella*, other *Bacteroides* species, enterococci, group C haemolytic streptococci and Enterobacteriaceae were also encountered in the deepest layer (level 3)
Brook and Frazier (1999) [37]	17 patients Aspirates or swabs	Axilla	*S. aureus*, *Peptostreptococcus prevotii*, *Streptococcus pyogenes* and *Prevotella melaninogenica*
Jemec et al. (1996) [38]	41 patients Aspirates	Axilla, inframammary fold and genital region	*S. epidermidis, S. aureus* and polymicrobial culture
Highet et al. (1988) [39]	32 patients Swabs	Perineal region	*Streptococcus milleri*, *S. aureus* and anaerobic streptococci

Table 3 Gut microbiome and HS

Paper	Participants	Methods	Main findings
Kam et al. (2020) [40]	3 patients and 3 controls	Faecal samples and 16S	Increased abundance of *Bilophila* and *Holdemania*; decreased abundance of Firmicutes, *Lachnobacterium* and *Veillonella* in patients with HS compared to controls
Eppinga et al. (2016) [41]	17 HS, 17 HS and IBD, 29 psoriasis, 31 IBD and 13 psoriasis and IBD patients and 33 controls	Faecal samples and quantitative polymerase chain reaction	Intestinal microbiome in the psoriasis, IBD, psoriasis and IBD, and HS and IBD groups was characterised by a decrease in *Faecalibacterium prausnitzii* and increase in *E. coli*, but that this was not seen in the HS-only group

immunofluorescence (IF) and fluorescence in situ hybridisation (FSH), which demonstrated the presence of biofilms, some of which were associated with *P. acnes* [2]. However, Ring et al. found a reduction in *P. acnes* in involved HS tissue compared to control [25].

Only two studies were identified which investigated the gastrointestinal microbiome in HS.

Eppinga et al. found no decrease in *F. prausnitzii* or increase in *E. coli* in participants with HS in comparison to the other included groups, none of which included healthy controls [41]. Kam et al. found an increased abundance of *Bilophila* and *Holdemania* and decreased abundance of Firmicutes, *Lachnobacterium* and *Veillonella* in patients with HS compared to controls [40]. However, this study was very small, with only three participants each in the HS and control groups.

Relevance of the Findings

Both *Porphyromonas* and *Prevotella* are most prevalent organisms on mucosal surfaces, including in the oral cavity, colon and tongue [42]. *Porphyromonas* and *Prevotella* in the skin microbiome may contribute to the pathogenesis of HS through upregulation of antimicrobial peptide (AMP) secretion, which in turn increases keratinocyte proliferation and recruitment of macrophages and neutrophils [43]. *Porphyromonas gingivalis* is an oral periodontopathogen and is implicated in the pathogenesis of periodontitis. Relevant virulence factors in HS include biofilm formation and dipeptidyl peptidase 4 activity [44]. *Prevotella* largely activates T helper 17 (Th17) immune responses, and has been shown to increase production of IL-23 and IL-1, both of which are implicated in the pathogenesis of HS [45–47]. Riverain-Gillet et al. demonstrated the presence of *Porphyromonas* and *Prevotella* in normal controls, but only in 22% of this group (as an anaerobic cluster) in comparison to 61% of affected individuals [21]. Ring et al. did not find the presence of *Porphyromonas* in normal controls [25].

Interestingly, whilst HS tunnels and Crohn's disease (CD) fistulas occur in similar anatomical sites such as the perineum, there are differences in the microbial composition between the two [48]. HS tunnels, as demonstrated by Ring et al., are characterised by an increase in *Porphyromonas* and *Prevotella*, as well as the presence of biofilms [23, 48]. In comparison, CD tunnels are characterised by an increase in adherent-invasive *E. coli*, staphylococci, *Streptococcus* and *Corynebacterium* species, in addition to reduced gut microbial diversity [48].

Staphylococcus aureus has previously been implicated in the pathogenesis of HS [38]. However, the role of *S. aureus* is now less clear. Dinh et al. found that individuals with HS were less likely to have *S. aureus* nasal colonisation than controls [49]. Katoulis et al. demonstrated no statistically significant increase in *S. aureus* nasal carriage in patients with Hurley stage III HS compared to those with stage I or II disease [50]. *S. aureus* has a clearer relationship with other skin diseases such as atopic dermatitis, where high rates of nasal carriage and clinical improvement after decolonisation are observed [51].

Unaffected skin in patients with HS has been shown to demonstrate alterations in the cutaneous microbiome in comparison to controls [21, 25]. This suggests that changes in the composition of the local microbiome may precede and contribute to development of lesions, rather than altering the local microbiome via secondary colonisation. The cutaneous microbiome is also influenced by host immunity; alterations in the local microbiome have been demonstrated via inhibition of complement 5a (C5a) receptor [52].

The role of diet in skin disease suggests a relationship between the gut microbiome and skin disease, a skin–gut axis. A well-recognised example is the relationship between coeliac disease and dermatitis herpetiformis [53]. Metabolic syndrome, and by association a Western diet, is a common co-morbidity in HS [54]. As described in Table 2, Eppinga et al. demonstrated an alteration in the gut microbiome in the HS and IBD group [41]. However, only a single Hurley stage III patient was included in the HS and IBD group, and none in the HS-only group. A small-scale study of patients with HS positive for anti-*Saccharomyces cerevisiae* antigen (ASCA) IgG who underwent surgical management of lesions and were subsequently placed on a brewer's yeast-free diet were found to have remission of lesions whilst practising dietary avoidance [15, 55]. A later study involving 37 patients following a yeast-exclusion diet for 6 years demonstrated that 70% of patients improved with no other treatment, and

consumption of yeast-containing foods was temporally associated with development of symptoms [56]. Elevated levels of ASCA IgG and IgA have been identified in patients with HS, particularly those with severe disease, in comparison to patients with psoriasis and healthy controls [57]. ASCA positivity is associated with IBD, and IBD is a recognised co-morbidity of HS [58, 59]. The relationship between ASCA, IBD and HS requires further exploration. Additionally, given the role of lifestyle modification in HS, such as weight loss and regular gentle exercise, the relationship between *Saccharomyces cerevisiae* dietary avoidance and HS should be elucidated further through larger-scale studies as a potential low-risk intervention.

As discussed by Frew et al., the cutaneous and gastrointestinal microbiome is thought to contribute to the pathogenesis of HS through multiple pathways including production of metabolites, simulation of myeloid dendritic cells via G protein coupled receptors, and as a triggering event to inflammation in predisposed individuals [60]. One study examining the peripheral blood bacterial composition of patients with HS and healthy controls found no significant difference [61]. This reinforces that any role of the gut or oral microbiome does not work directly via haematogenous spread, but rather through alterations in metabolic, immunological and inflammatory pathways.

The role of the microbiome in the pathogenesis of HS remains unclear. There is evidence that inflammation is the triggering event to follicular occlusion and subsequent follicular rupture and fistula formation [62]. Whether the dysbiosis and alternations in the local microbiome are pathogenic and a driver in the underlying inflammatory processes, or a result, remains to be elucidated.

LIMITATIONS

Defining what constitutes the "normal" cutaneous microbiome is an evolving area. The microbiota predominantly vary by anatomical location on the skin, rather than ethnicity or the use of common topical products [63]. The Human Microbiome Project is a large-scale microbiome study aimed at characterising the "normal" human microbiome across a number of anatomical environments including the skin [64, 65]. It is unlikely that a true normal microbiome exists, and it is likely to be varied within and across individuals at various stages of time. Therefore, comparisons with "normal healthy" controls may introduce identification bias into interpretation of the results.

There are many limitations of microbiome research in HS. Only a few studies in this review included patient demographic data such as smoking status and body mass index (BMI). Smoking has been demonstrated to have an effect on the intestinal microbiome, causing reduced diversity and alterations to the composition of commensal bacteria [66]. The intestinal microbiome in some studies has been found to be altered in comparison to individuals with a normal BMI [67]. However, no studies to date have examined the relationship between these factors and the microbiome in HS. Microbiome studies should include sufficient metadata in relation to age, sex, ethnicity, disease severity, anatomical location, concomitant medication, prior or concurrent antibiotic use and topical product use [68].

There was heterogeneity in the methodology employed across the studies included in this review article. Not all studies included information regarding patient demographics or disease severity. There was variation in the way that specimens were obtained (swabs, aspirates and/or biopsies) and the identification of bacteria was made (either cultures or metagenomics). It has been shown that there is variation in the bacteria identified on normal skin on swabs versus biopsies using 16S [69]. In that study by Prast-Nielsen et al., there was increased number of anaerobes identified on skin biopsy, such as *Bacteroides*, which likely reflects the composition of bacteria found in the dermis versus superficial sampling of the epidermidis or open lesions with swabs alone. This has implications in interpreting the results of findings of microbiome studies, as many studies have only included swabs. One study by Lapins et al. used CO_2 laser to systematically remove layers of skin, and swab as they went down [36].

This demonstrated the presence of coagulase-negative *Staphylococcus* in the deeper layers, which are implicated in biofilm formation in HS [70]. This is important as the cutaneous microbiome extends as far down as the superficial subcutis—therefore inclusion of skin biopsies in future studies is important in capturing the true microbiome of the skin cross-sectionally.

Whilst cultures are an important tool in identification of bacteria, particularly in clinical settings, they have several limitations. It is estimated that 99% of bacteria cannot be grown on culture [71]. However, cultures remain important in research as adjuncts to newer methodologies such as metagenomics, in order to assist with interpretation of metadata and for contributing vital information to reference databases [72]. Additionally, cultures are a cost-effective and non-invasive testing methodology in clinical practice, and inclusion of these in research is important to provide clinically relevant information for future practice.

Many studies used unaffected sites for culture or biopsy as part of their study protocol. However, as discussed by Frew et al., the definition of lesional, perilesional and non-lesional skin in HS is not standardised. Given the morphology of HS, with subcutaneous tunnels and fistulas, careful identification of uninvolved skin is required to avoid inadvertent sampling of affected tissue. As Frew further discusses, healthy controls should be matched as close as possible in relation to anatomical site, age, sex, smoking status and ethnicity [73].

The use of 16S is beneficial in identifying the presence of an array of bacteria in comparison to the traditional method of bacterial culture. However, this technology does not identify all bacteria present, bacterial activity, nor host response [74]. It is a useful tool in examining some of the populations of bacteria implicated in cutaneous disease but is unable to shed light on the interactions between host and microbe. Further research using whole genome sequencing and RNA transcriptomics responses should be undertaken to better elucidate bacterial activity and the interplay between organism and host gene expression. Furthermore, standardised approaches to collection of affected and unaffected tissue within and across participants, and collection of associated baseline patient data, are crucial in interpretation of data and in minimising confounding factors [68]. Skin microbiome research is vulnerable to factors such as a collection methodology, storage, contamination and biases introduced via sequencing methods [75].

Biofilms and their role in disease pathogenesis of HS were outside of the scope of this review article but are deserving of mention in this discussion. It has been established that HS is a disease characterised by biofilm formation, which may be a significant trigger in the organism–host pathophysiological response [76, 77]. Ring et al. demonstrated the increased bacterial aggregates via PNA-FSH in chronic HS lesions, and the presence of biofilms in both lesional and perilesional tissue [77]. Several bacteria have been shown to have biofilm formation as an established virulence factor, such as *Porphyromonas* and *S. epidermidis* [44, 78]. The treatment resistance of HS to antibiotics, particularly in moderate to severe disease, may be in part due to the presence of biofilms [12].

IMPLICATIONS FOR FUTURE RESEARCH

The influence of treatment on the local microbiome is an area worthy of exploration. Adalimumab is an anti-TNFα which has been shown to be an effective treatment in the treatment HS [79]. Studies have demonstrated that treatment with adalimumab causes alterations in the gut microbiome towards eubiosis in patients with CD [80, 81]. Treatment of psoriasis with biologics has been demonstrated to cause alterations in the local microbiome, shifting it back towards the microbial composition of healthy controls [82]. However, alterations to the oral, gut and cutaneous microbiome in patients with HS undergoing treatment (including with biological agents) have not yet been investigated. This may help identify if the cutaneous and gastrointestinal microbiome alter with treatment, and whether this precedes or follows clinically measurable improvement in skin lesions. On the basis of research in CD and psoriasis, we would anticipate that an alteration

towards eubiosis in the cutaneous and gastrointestinal microbiome in HS would be demonstrated. However, whether changes towards eubiosis will be accompanied by clinical response in patients with HS to treatment remains to be known.

No studies have yet been conducted examining the oral microbiome in HS, and research should be targeted at this branch of microbiome research. The oral microbiome is understood to be implicated in systemic illnesses such as heart disease and gastrointestinal cancer [83, 84]. Periodontitis has been shown to be associated with psoriasis, pemphigoid and pemphigus [19].

Likewise, there has been very limited research into the role of the gastrointestinal microbiome in HS, with the exception of the two studies discussed in this paper.

Given the propensity for HS to affect the inguinal and genital area, future research examining alterations in the vaginal microbiome should be undertaken. This may help shed light on whether there is cross-colonisation between the vaginal mucosa and HS lesions, and in which direction that this may occur. Additionally, further comparative research between HS tunnels and CD fistulas may help identify potential shared underlying pathways of pathogenesis, given the propensity for both diseases to occur within the perianal and genital regions.

Psychiatric co-morbidities, such as depression and anxiety, are common in HS [85]. Whether these occur as a consequence of the physical and social difficulties associated with HS, or as a result of associated underlying systemic inflammation, remains unclear. As discussed previously, collection and analysis of metadata with the microbiological findings should be undertaken. This would assist with identifying if specific microbial populations and compositions are associated with co-morbid psychiatric diseases in patients with HS. This may help identify possible therapeutic targets for patients with a high burden of psychological illness in the setting of HS.

As discussed, future studies examining the cutaneous microbiome of HS should include both biopsies for NGS and swabs or aspirates for traditional culture methods, and use metagenomics where possible, with a view to the implementation of whole genome sequencing and transcriptomics. The use of swabs and traditional culture methods is important to continue to include in future research, given that this represents a low-cost and mostly non-invasive test for future clinical practice when assessing alterations in the microbiome before and after treatment as potential markers of treatment response. Examining the oral, gastrointestinal and cutaneous microbiomes concurrently in individuals with and without HS would assist in understanding the alterations towards dysbiosis, and potentially provide targets for future therapeutic interventions.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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