Cutaneous and Gut Dysbiosis in Alopecia Areata: A Review

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Alopecia areata (AA) is a common, immune-mediated nonscarring alopecia. Breakdown of immune privilege combined with local immune cell infiltration is central to the development of AA; yet, the instigating factors causing immune dysregulation remain elusive. Recent attention has focused on the microbiome in AA, where alterations to the usual composition of healthy microorganisms is observed. This review examines the current evidence for bacterial dysbiosis affecting the scalp and gut of patients with AA and summarizes the potential influence of altered microbial composition on immune dysregulation in AA. Although the literature supports changes to the bacterial composition of patients with AA, a causal link between microbial dysbiosis and AA pathogenesis remains to be established.

Keywords: Alopecia areata, Dysbiosis, Immune privilege, Microbiome

INTRODUCTION

Alopecia areata (AA) is a chronic, autoimmune condition characterized by nonscarring (noncicatricial) hair loss (Pratt et al, 2017) affecting 2% of the population worldwide (Wang et al, 2022; Zhou et al, 2021). It classically presents as a small, annular patch of hair loss to the scalp but can progress to more severe subtypes such as alopecia totalis (hair loss to the entire scalp) or alopecia universalis (hair loss to all hair-bearing regions) (Pratt et al, 2017). Disease onset typically occurs during the third or fourth decades of life but may affect patients of any age (Villasante Fricke and Miteva, 2015). Severity of AA at time of presentation is correlated with disease prognosis, suggesting that persistent disease is more likely to occur in patients presenting with more total hair loss, including in pediatric patients (Rangu et al, 2019; Rocha et al, 2011; Villasante Fricke and Miteva, 2015). The unpredictable course of AA induces significant psychosocial and emotional burden on patients and caregivers, with increased prevalence of psychiatric comorbidities in patients with AA, including mood and adjustment disorders (Rencz et al, 2016; Torales et al, 2022; Villasante Fricke and Miteva, 2015).

Disease pathogenesis of AA is complex and involves immune-mediated attack and breakdown of immune privilege at the hair follicle (Anzai et al, 2019). Differences in genetic loci involved in immune function have been implicated (Barahmani et al, 2008; Pratt et al, 2017). Recently, aberrations in the cutaneous and gut microbiome have been described in AA (Constantinou et al, 2021). The composition of the microbiome is different between patients with AA and healthy controls (Won et al, 2022), and the presence of strict anaerobic bacteria suggests hypoxic conditions within AA hair follicles (Pinto et al, 2020b, 2019). Although a role for the microbiome in AA has garnered increasing attention over recent years, the current evidence remains at a nascent stage and requires further delineation to demonstrate a causal link between microbial dysbiosis and AA.

MICROBIOME

The skin continuously interacts with the environment and is host to a wide range of bacteria, archae, viruses, fungi, and mites (Kong, 2011). Together, these microorganisms comprise the cutaneous microbiome. Composition of the microbiome is established prenatally (Jiménez et al, 2005) and is impressionable early in development, becoming more stable or 'fixed' as an individual progresses toward adulthood (Capone et al, 2011; Monir and Schoch, 2022). In general, a diverse array of microbial species is considered beneficial (Monir and Schoch, 2022), and composition of the microbiome is influenced by anatomy, genetics, and the host environment (Grice and Segre, 2011). Anatomical differences in the cutaneous microbiome are due to variations in pH, skin temperature, humidity, and sebaceous gland density, thereby creating 'cutaneous niches' (Grice and Segre, 2011). The skin surface is acidic (pH 5), which favors the growth of commensal bacterium, such as coagulase-negative *Staphylococcus* (ie, *Staphylococcus epidermidis*) and *Corynebacterium* (Elias, 2007), while inhibiting the growth of *Staphylococcus aureus* (*S aureus*) and *Streptococcus pyogenes* (Korting et al, 1990).

The skin is both a physical and immunological barrier. Microorganisms inhabit the skin and assist with barrier defenses through a variety of mechanisms, such as competing

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Abbreviations: 5-ASA, 5-aminosalicylic acid; AA, alopecia areata; AD, atopic dermatitis; IBD, inflammatory bowel disease; MHC, major histocompatibility complex; PSM, phenol-soluble modulin; rRNA, ribosomal RNA; SALT, Severity of Alopecia Tool; SCFA, short-chain fatty acid; Th, T helper; Treg, regulatory T cell

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for habitat with pathogenic organisms (Borkowski and Gallo, 2011), releasing molecules that kill and inhibit pathogens (Cogen et al, 2010), and modulating the host immune response (Lai et al, 2009). *S epidermidis*, a commensal bacterium, modulates the host innate immune response through the production of phenol-soluble modulins (PSMs) (Cogen et al, 2010). These PSMs exert antimicrobial action against pathogenic bacteria, including *S aureus* and Group A *Streptococcus* while preserving normal skin flora (Borkowski and Gallo, 2011; Cogen et al, 2010). As such, commensal bacteria exert the specific and desirable effect of inhibiting pathogenic organisms; alterations to skin flora, including these commensals, may perturb normal immune defenses, allowing the growth of pathogenic microorganisms.

In addition to skin microbiota, the composition and function of gut microbiota modulate the cutaneous immune responses through the "gut–skin axis" (Salem et al, 2018). Two hypothetical mechanisms are proposed to explain how gut microbiota influence skin homeostasis: (i) modulation of systemic immunity (ie. facilitation of both pro and anti-inflammatory immune responses depending on gut microbiota composition) (Forbes et al, 2016; O'Neill et al, 2016) and (ii) direct metastases of gut microbiota and metabolites to cutaneous sites (O'Neill et al, 2016; Samuelson et al, 2015). These mechanisms may partially explain why gastrointestinal diseases are associated with cutaneous manifestations and why aberrations in the gut microbiome are associated with inflammatory skin diseases, such as atopic dermatitis (AD) and psoriasis (Salem et al, 2018).

Microbiome in skin disease

Alterations in the composition of the cutaneous or gut microbiome (referred to as dysbiosis) are often associated with a dysregulated immune response and development of skin disease (Borkowski and Gallo, 2011). Dysbiosis is implicated in skin conditions, including AD, psoriasis, acne vulgaris, and other inflammatory conditions of the hair follicle described below.

Patients with AD demonstrate bacterial dysbiosis, specifically a decrease in cutaneous bacterial diversity and an increase in *S aureus* (Geoghegan et al, 2018; Kobayashi et al, 2015). Patients with AD colonized by *S aureus* display greater barrier dysfunction, allergen sensitization, and disease severity than those who are not colonized (Simpson et al, 2018). Dysbiosis is present during flares and at baseline; however, the mechanism through which alterations in the cutaneous microbiome promote AD remains unclear. Eczematous plaques often present at stereotypical sites (ie, antecubital and popliteal fossa in adults, extensor surfaces of the arms and legs in infants), which might suggest that microorganisms favor 'cutaneous niches' and play a role in predisposition to AD lesions at these sites. Treatment of AD alters the cutaneous microbiome, with increased proportions of *Streptococcus*, *Propionibacterium*, and *Corynebacterium* (Kong et al, 2012). Increased bacterial diversity is observed after corticosteroid or bleach bath therapy in pediatric patients (Gonzalez et al, 2016) and after corticosteroid plus antihistamine therapy in adult patients (Guzik et al, 2005). Moreover, there is an association between AD and AA (Lee et al, 2019; Mohan and Silverberg, 2015), with evidence that history of AD increases the risk of developing severe AA in children (Sorrell et al, 2017). Certainly, alteration of barrier function in AD provides a nidus of entry for bacteria into the deeper skin compartments (such as the hair follicle), but whether bacterial dysbiosis is exacerbated in AA patients with AD requires further investigation.

Cutaneous and gut dysbiosis is also observed in patients with psoriasis. Alterations in the gut microbiome cause aberrations in metabolism and metabolic biproducts, contributing to a psoriasis phenotype (Myers et al, 2019). Analysis of the cutaneous microbiome reveals increased proportions of *Streptococcus* and decreased proportions of *Staphylococcus* species in patients with psoriasis compared to healthy controls (Fahlén et al, 2012). In addition, the association between early childhood infections and development of pediatric psoriasis (Chen et al, 2021; Garritsen et al, 2017) further suggests an important role for microorganisms in the pathogenesis of psoriasis.

Hair follicle–associated skin diseases also exhibit cutaneous dysbiosis. Proliferation of *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) is central to the pathogenesis and treatment of acne vulgaris. *C acnes* is the predominant skin commensal bacterium within the pilosebaceous units of individuals with and without acne vulgaris (representing 87% of abundant species in both groups), but different strains are present in patients with acne-prone skin versus in healthy skin (Fitz-Gibbon et al, 2013). Many acne therapies target alterations in the microbiome, such as topical antibiotics and isotretinoin, which decrease the inflammatory response to *C acnes* (Dispenza et al, 2012). Moreover, patients with acne showed decreased Actinobacteria and increased Proteobacteria within samples of gut microbiota, suggesting that gut dysbiosis may also contribute to the pathogenesis of disease (Yan et al, 2018). Dysbiosis is also reported in other skin follicle–associated conditions such as seborrheic dermatitis, where increased proportions of *Malassezia*, *Staphylococcus*, and *C acnes* are commonly observed (Clavaud et al, 2013; Wang et al, 2015; Xu et al, 2016). Hidradenitis suppurativa, a chronic hair follicle–associated inflammatory skin disease, is often linked to biofilm-forming bacteria (ie, coagulase negative *Staphylococcus*) causing inflammasome activation and release of proinflammatory cytokines (Vekic et al, 2018). Similarly, *S aureus* is commonly isolated from patients with untreated folliculitis decalvans, with remission observed after treatment with oral antibiotics (Constantinou et al, 2021). The pathogenesis of folliculitis decalvans is felt to involve cytotoxic proteins secreted from *S aureus* that stimulate T-cell and neutrophil migration, epithelial damage, and release of proinflammatory cytokines (ie, IFN-g and TNF-α) (Chiarini et al, 2008).

MECHANISMS OF IMMUNE DYSREGULATION IN AA

Since AA was first described, numerous theories have been proposed to explain the mechanistic cause, including toxic exposures, physical trauma and psychological stress, and neuropathic or endocrine disturbances (Broadley and McElwee, 2020; Pratt et al, 2017; Walker and Rothman, 1950). In 1958, Rothman and colleagues first proposed an autoimmune theory of AA (Van Scott and Ekel, 1958). Since

then, a catalog of support has grown for the autoimmune hypothesis, including strong associations between AA and other autoimmune conditions (vitiligo, inflammatory bowel disease [IBD], thyroid disease), response to immunomodulatory therapies, and preclinical and clinical studies supporting dysregulated immune attack on hair follicles (Barahmani et al, 2009; Chu et al, 2011; Xing et al, 2014).

Notably, the pathogenesis of AA was, at one time, linked to infectious agents. The infectious hypothesis of AA was first proposed in the mid-19th century (Broadley and McElwee, 2020) but gradually fell from favor owing to the inability to transmit AA with direct inoculation (Sabouraud, 1896) and suspicion that prior cases were tinea capitis misdiagnosed as AA (Broadley and McElwee, 2020; Callander and Yesudian, 2018). Despite this, the hypothesis that AA is connected to an infectious etiology occasionally resurfaces, such as detection of cytomegalovirus DNA in lesions of AA (Skinner et al, 1995) and recent reports of association between AA and COVID-19 infections (Kim et al, 2024). The prevailing hypothesis still suggests an autoimmune etiology of AA; however, it remains plausible that the increase in immune activity may be exacerbated by secondary infection, such as through mechanisms of antigen epitope mimicry (Broadley and McElwee, 2020).

The anagen bulb and bulge regions of the hair follicle are immune privileged, meaning that autoantigens present in the hair follicle are shielded from immune recognition by creation of a local anergic state (Bertolini et al, 2020). Immune privilege is accomplished through a variety of mechanisms, such as physical barriers to exclude invading immune cells (extracellular matrix, lack of lymphatic drainage) (Ito et al, 2004; Paus et al, 2003), proapoptotic ligands present on dermal papilla cells (Ferguson and Griffith, 2006; Wang et al, 2014), and expression of factors ("immune privilege guardians") that inhibit major histocompatibility complex (MHC) class I expression (Ito et al, 2004). In combination, these mechanisms downregulate the expression of MHC-I, inhibiting immune cell recruitment and the production of IFN-γ, a known cytokine inducer of MHC expression (Kinori et al, 2012; Mcdonagh et al, 1993; Meyer et al, 2008).

Numerous studies have also demonstrated the importance of $CD8^+NKG2D^+$ T cells and release of IFN-γ in AA. In mouse models, patches of hair loss are observed after subcutaneous injection of $CD8^+$ T lymphocytes into C3H/HeJ mice (McElwee et al, 2005), demonstrating that $CD8^+$ T cells are sufficient for the development of an AA phenotype. $CD8^+NKG2D^+$ T cells release IFN-γ through the activation of JAK signaling cascades, leading to immune privilege collapse at the hair follicle, exposure of autoantigens to $CD8^+NKG2D^+$ T cells, and escalation of the autoimmune attack on the hair follicle (Xing et al, 2014). This disrupts the function and growth cycle of the hair follicle, leading to premature hair loss and inhibition of growth. Despite advances in our mechanistic understanding of AA, the instigating factors leading to initial IFN-γ release from T cells and NK cells remain poorly understood. It is hypothesized to occur secondary to breakdown of immune privilege at the hair follicle or owing to local environmental or physical stressors, including microbial dysbiosis.

MICROBIOME IN AA

Over the past decade, accumulating evidence suggests a role for the cutaneous and gut microbiome in the disease pathogenesis of AA (Figure 1). The increasing utility of 16S ribosomal RNA (rRNA) metagenomic sequencing has expanded the current knowledge of bacterial and archaeal species present in cutaneous niches (Lu et al, 2021; Rinaldi et al, 2022b). This is particularly relevant for hair follicles and sebaceous glands which produce anoxic environments, as anaerobes are challenging to isolate in typical culture-based approaches given their specific growth parameters and slow growth (Constantinou et al, 2021; Grice and Segre, 2011).

Breakdown of immune privilege leads to vulnerability of the hair follicle during the anagen phase of the hair growth cycle (Bertolini et al, 2020), and it is hypothesized that local alterations in microbiota may contribute to hair follicle vulnerability during anagen. There are various hypotheses regarding how changes in the microbiome may contribute to the pathogenesis of AA, such as exacerbating premature catagen phase, collapse of immune privilege, or promotion of miniaturization of hair follicles (Lousada et al, 2021). Alternatively, primary inflammation within the hair follicle may lead to dysbiosis. Herein, we explore the current data regarding the role for the microbiome in AA.

Cutaneous microbiome in AA

Over the past decade, a handful of studies have explored changes in the composition of bacterial species present on the scalp of patients with AA (Table 1). The initial observations were reported by Pinto et al (2019), who examined the microbial composition of the scalp in patients with AA (n = 15) using superficial swabs, and compared these findings with those of healthy individuals (n = 15). Their results indicated an overall increase in alpha diversity (Shannon index) in patients with AA. Further quantitative analysis targeted at the main bacterial species found on the scalp (*C acnes, S epidermidis, S aureus)* revealed a significant increase in *C acnes* abundance and decrease in *S epidermidis* abundance in patients with AA compared to controls, with no significant changes in the relative abundance of *S aureus* (Pinto et al, 2019). On the basis of these findings, the authors proposed altered balancing between *C acnes* and *S epidermidis* might be significant in AA, prompting other researchers to suggest a protective role for *S epidermidis* in development of AA (Lousada et al, 2021).

Further studies explored the scalp microbiome in patients with AA stratified by disease severity. Won et al (2022) collected superficial swabs from patients with AA (n = 33) and healthy controls (n = 12) and analyzed the microbial composition relative to AA severity (determined by hair loss percentage, disease progression, treatment response, and symptom duration). They found a significant increase in alpha diversity in all patients with AA, although this effect was diminished when adjusting for disease severity. Moreover, there were no significant differences in overall bacterial community structure and phylogenetic diversity (beta diversity assessed by Bray–Curtis distance) between patients with AA and controls (Won et al, 2022). Closer examination of the bacterial composition of the scalp using 16S rRNA sequencing revealed patients with severe AA had decreased

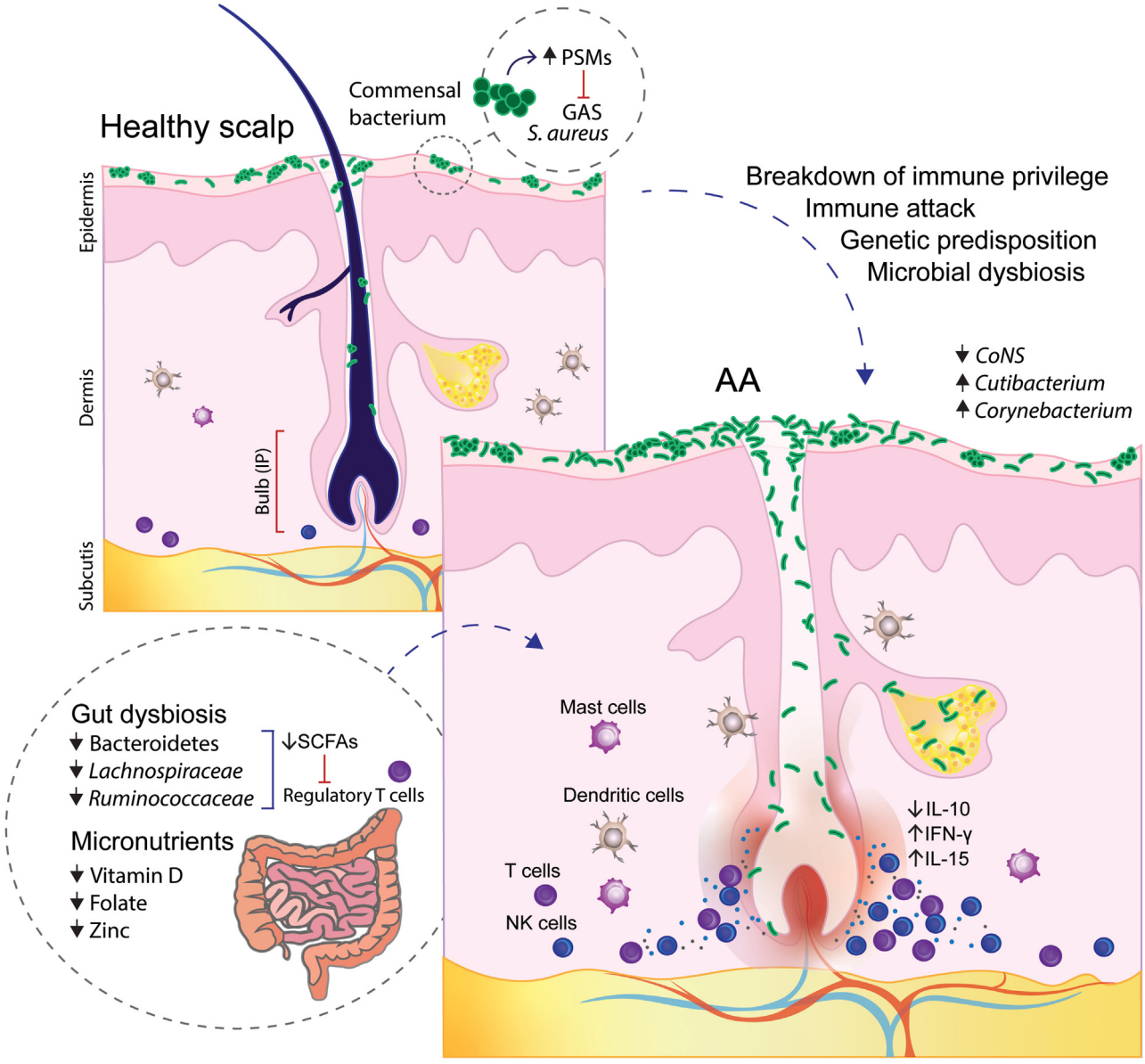

Figure 1. Hypothesized mechanisms of microbial dysbiosis in AA. The pathogenesis of AA is multifactorial, including IFN-γ release through T cells and NK cells, IP collapse, and autoimmune attack on the hair follicle. Commensal bacterium on the healthy scalp assist with barrier defenses through mechanisms such as release of PSMs, which inhibit pathogenic organisms (GAS, *S aureus*). Superficial swabs from patients with AA show increased abundance of *Cutibacterium* and *Corynebacterium* and decreased CoNS. Skin punch biopsies from patients with AA demonstrate increased expression of inflammatory and proapoptotic markers. The "gut–skin axis" also modulates cutaneous immune responses and becomes dysregulated in AA. Patients with AA exhibit decreased abundance of Bacteroidetes, *Lachnospiraceae*, and *Ruminococcaceae*, which are important producers of SCFAs. AA, alopecia areata; CoNS, coagulase-negative Staphylococci; GAS, group A Streptococcus; IP, immune privilege; PSM, phenol-soluble modulin; SCFA, short-chain fatty acid.

proportions of *S caprae* among all *Staphylococcus* species (10.5% in patients with severe AA compared with 42.1% in patients with mild AA and 49.5% in healthy controls) and increased overall proportions of *Corynebacterium* (6.3% in patients with severe AA compared with 0.6% in those with mild AA and 0.3% in healthy controls). Moreover, they found increased proportions of *Cutibacterium* species to *S caprae* ratio (16.01% in those with severe AA vs 2.13% in those with mild AA and 0.97% in healthy controls) (Won et al, 2022). They did not find increased proportions of the *C acnes*/*S epidermidis* ratio or *C acnes*/*S aureus* ratio in patients with AA, as previously reported (Pinto et al, 2019), instead suggesting that the *Cutibacterium*/*S caprae* ratio may better predict prognosis or susceptibility to severe AA. Indeed, increased proportions of *Cutibacterium* may cause an inflammatory response within the pilosebaceous unit, similar to acne vulgaris, but this mechanism requires further investigation. Differences in observed microbial populations between the study by Pinto et al (2019) and those by Won et al (2022) may be partially explained by patient demographics and exclusion criteria reported in each study. Exclusion criteria specified by Pinto et al (2019) included no use of topical therapies (3 months), immunosuppressants (3 months), antibiotics (30 days), or probiotics (15 days)

Table 1. Studies Examining the Cutaneous Microbiome in AA

Reference	Study Design	AA Patient Characteristics	Comorbidities and Exclusion Criteria	Sampling Method	Identification Method	Reported Changes in AA
Pinto et al (2019)	Cross-sectional, n = 30 (15 AA, 15 HCs), Italy	Age range = 20–60 y; 60% female; not disclosed: age of disease onset, disease duration, and severity of AA	Patients with dermatologic comorbidities excluded; no topicals or immunosuppressants (3 mo), antibiotics (30 d), or probiotics (15 d) prior to sample collection	Superficial swabs (n = 30) and skin biopsy (n = 4)	16S rRNA, qRT-PCR	Superficial swabs: increased alpha diversity and abundance of *C acnes*, decreased abundance of *S epidermidis* Biopsy: Actinobacteria (increased epidermis, decreased dermis), Bacteroidetes (increased all compartments), Proteobacteria (increased dermis and subcutis), and Firmicutes (increased subcutis)
Pinto et al (2020a)	Cross-sectional, n = 47[1] (26 AA versus 21 HCs), Italy	Age range = 20–60 y; 60% female; SALT S2–S5; not disclosed: age of disease onset and disease duration	Patients with dermatologic comorbidities excluded; no topicals or immunosuppressants (3 mo), antibiotics (30 d), or probiotics (15 d) prior to sample collection	Superficial swabs (n = 47) and skin biopsy (n = 8)	16S rRNA, qRT-PCR	No significant change to alpha diversity Increased *Cutibacterium*, decreased *S epidermidis* Increased expression of TNF-α, FAS, KCNA3, and SOD-2 in epidermis and dermis and decreased NOD-2 from biopsy samples
Won et al (2022)	Cross-sectional, n = 45 (33 AA (26 mild, 7 severe); 12 HCs), Korea	Age range = 9–60 y; 33% female; median disease duration: mild AA = 151.5 d, severe AA = 746 d; age of disease onset not specified	6 patients with AA with unspecified autoimmune disorders (unspecified in HC group); no exclusion criteria for treatment with topical therapies, antibiotics, or probiotics; comorbid dermatologic conditions not disclosed	Superficial swabs	16S rRNA	Increased alpha diversity, effect lost in subgroup comparison by severity Severe AA: increased *Corynebacterium* and *Cutibacterium* species and decreased *S caprae*
Rinaldi et al (2022a)	Cross-sectional, n = 4[1] (2 AA, 2 HCs), Italy	Age range = 20–60 y; not disclosed: sex, age of disease onset, disease duration, and severity of disease	Patients with dermatologic comorbidities excluded; no topicals or immunosuppressants (3 mo), antibiotics (30 d), or probiotics (15 d) prior to sample collection	Skin biopsy (4-mm punch), 2 samples collected from each participant	16S rRNA, TEM, and gram staining	Increased alpha diversity Decreased *Firmicutes* (all levels) and *Staphylococcus* (subcutis); increased Proteobacteria (dermis, subcutis) and Bacteroidetes phyla (subcutis) Bacteria inside outer root sheath (level of isthmus) and dermal papilla

Abbreviations: AA, alopecia areata; HC, healthy control; rRNA, ribosomal RNA; SALT, Severity of Alopecia Tool; TEM, transmission electron microscopy.
[1]Sample size includes same samples from Pinto et al (2019).

prior to sample collection. In contrast, no exclusion criteria were required by Won et al (2022). Moreover, Pinto et al (2019) excluded participants with any disease comorbidities, whereas Won et al (2022) included 6 patients with AA and unspecified autoimmune conditions.

Exogenous compounds, such as nucleic acids, proteins, virus particles, and engineered particles, may access the hair follicle through tight junction proteins expressed by keratinocytes, specifically during anagen phase when these barriers become 'less tight' (Vogt et al, 2020). Consequently, surface samples obtained by superficial swabs may not accurately represent the microbial changes occurring deeper in the hair follicle. This issue of microbial penetration into deeper skin compartments was addressed by Pinto et al (2019), who obtained skin punch biopsies from the scalp of patients with AA (n = 2) and healthy controls (n = 2) to examine bacterial abundance in discrete layers of the skin. They found higher proportions of Actinobacteria and Bacteroidetes in the epidermis of patients with AA, whereas the dermis showed decreased Actinobacteria and increased Proteobacteria and Bacteroidetes. The subcutis in patients with AA had increased proportions of Proteobacteria, Firmicutes, and Bacteroidetes compared with those of controls (Pinto et al, 2019). Notably, *Akkermansia muciniphilia*, a strict anaerobe, was found in deep biopsies from patients with AA (Pinto et al, 2019), suggesting possible hypoxic conditions within hair follicles that might explain the overgrowth of *C acnes* (Mayslich et al, 2021; Pinto et al, 2020b). Subsequent studies by Rinaldi et al (2022a) utilized optical and electron microscopy and Gram staining on the same biopsies collected by Pinto et al (2019) to show bacteria in the outer root sheath and deeper compartments of the dermal papilla. The presence of bacteria deep within the hair follicle was associated with infiltrating lymphocytes (Rinaldi et al, 2022a) and higher expression of inflammatory and apoptotic markers (TNF-α, FAS, KCNA3, SOD-2). Markers of bacterial chemotaxis, flagellar assembly, and cellular antigens were also detected in biopsy specimens from the epidermis and dermis of patients with AA compared to healthy controls (Pinto et al, 2020a). To summarize, alterations of the composition of the microbiome are present in AA hair follicles, but whether these differences play an active role in stimulating perifollicular inflammation, are simply incidentally present, or result from the local inflammation is not known.

Few studies have directly investigated the effects of modulating the cutaneous microbiome on treatment of AA. Probiotics can be applied topically and effectively colonize the skin (De Almeida et al, 2023; Mosaico et al, 2022); however, there is limited evidence for this mode of delivery, and application of live bacteria onto the skin leads to concerns such as opportunistic infections in immunocompromised hosts. Microorganisms within the gut produce metabolic byproducts, otherwise known as 'postbiotics,' composed of inanimate cellular components and metabolites without capability to colonize the host (De Almeida et al, 2023). As a result, there is increasing interest in topical application of postbiotics, which specifically include an array of enzymes, short-chain fatty acids (SCFAs), antimicrobial peptides, vitamins, and cell surface proteins isolated from the supernatant of probiotic cultures that may have antimicrobial and immunomodulatory effects (Tsilingiri and Rescigno, 2013). Indeed, complete hair regrowth was observed in 47.5% (38 of 80) of patients with AA treated with a gel containing biomimetic peptides (set to mimic the action of platelet-rich plasma) and postbiotics compared to 5% (4 of 80) in the placebo control (Rinaldi et al, 2020). In theory, postbiotics could be obtained from any bacterial culture, such as isolation of PSMs from *S epidermidis* cultures to inhibit pathogenic organisms. At this point, the field of topical probiotics or postbiotics remains in its infancy, but with additional investigations, could represent a valuable therapeutic option to modulate the cutaneous microbiome.

Gut microbiome in AA

To date, several studies have interrogated the role of the gut microbiome in AA (Table 2). The gut microbiota is a key modulator of systemic immunity, and imbalances (dysbiosis) in the microbiome are known to trigger several immune disorders through the activation of local and circulating T cells (ie, T helper [Th]17/regulatory T cell [Treg]) (Honda and Littman, 2016; Moreno-Arrones et al, 2020). SCFAs are the most common microbial metabolites in the intestine (Silva et al, 2020) and are known to promote the proliferation of Tregs directly influencing the systemic immune response (Luu et al, 2019). Butyrate, an SCFA, increases the proliferation and function of T cells and enhances the integrity of the intestinal barrier (Bach Knudsen et al, 2018; Luu et al, 2018). The phylum Bacteroidetes contains several bacteria that produce butyrate, and studies show a decrease in this protective phylum in patients with AA (Lee et al, 2024; Lu et al, 2021). Decreased abundance of Bacteroidetes in patients with AA leads to decreased butyrate production, promoting disruption (preventing enhancement) of the gut barrier, thereby exacerbating systemic inflammation (Hotamisligil, 2017). Similarly, *Lachnospiraceae* and *Ruminococcaceae* are important producers of SCFAs and are also reduced in the gut of patients with AA (Bain et al, 2022; Rangu et al, 2021). In addition, genes associated with AA impact colonization of gut microbiota and can induce a Th1 response leading to increased IFN-γ (De Pessemier et al, 2021).

Studies in C3H/HeJ mice have shown spontaneous development of AA with alterations in food composition, such as a diet rich in soybean phytoestrogens (McElwee et al, 2003). There are also reports of hair regrowth in 2 patients with alopecia universalis after fecal transplantation for recurrent *Clostridioides difficile* infections (Rebello et al, 2017) and report of hair regrowth in 1 elderly patient after fecal transplantation (Xie et al, 2019). Although studies analyzing stool composition of patients with AA compared to healthy controls did not reveal statistically significant differences in bacterial species richness (alpha diversity) of gut microbiota, the overall composition of gut microbiota was distinct (Bain et al, 2022; Lu et al, 2021; Moreno-Arrones et al, 2020). The presence of *Parabacteroides distasonis* and *Clostridiales vadin* BB60 group was predictive for AA in 80% of patients (Moreno-Arrones et al, 2020). Notably, some bacteria increased in patients with AA were observed in other inflammatory conditions, such as ankylosing spondylitis (Costello et al, 2015), indicating the shift

Table 2. Studies Examining the Gut Microbiome in AA

Reference	Study Design	AA Patient Characteristics	Comorbidities, Treatments and Exclusion Criteria	Sampling Method	Identification Method	Reported Changes in AA
Rebello et al (2017)	Case series, n = 2 AU, USA	Patient 1: 38 y, male, AU, disease duration 10 y Patient 2: 20 y, male, AU, disease duration 2 y	Crohn's disease (patient 2)	—	—	Hair regrowth in 2 AU patients after FMT for recurrent *C difficile* infections
Xie et al (2019)	Case report, n = 1 AA, China	86 y, male, AA, age of disease onset and disease duration not disclosed	—	—	—	Hair regrowth after FMT for gut dysbiosis
Moreno-Arrones et al (2020)	Cross-sectional, n = 30 (15 AU, 15 HCs), Spain	Mean age: AU 42.2 y, HC 37.9 y; AU 73.3% female, HC 20% female; 60% of HCs cohabituated with AU cases; not disclosed: age of disease onset and disease duration	All comorbidities excluded except hypothyroidism in AU patients (40% cases); all comorbid diseases excluded for HC; no oral or systemic immunomodulators (12 wk), extreme diets, yogurt, pre or probiotics (6 wk) prior to sample collection	Stool	16S rRNA	No significant difference in alpha or beta diversity Bacterial counts of *Parabacteroides distasonis* and *Clostridiales vadin BB60* predictive of AA
Lu et al (2021)	Cross-sectional, n = 68 (33 AA, 35 HCs), China	Mean age: AA 33.79 y, HC 37.31 y; AA 94.1% female, HC 84.2% female; 51.5% mild AA, 48.5% severe AA; disease duration: 60.6% ≤6 mo, 39.4% >6 mo	All comorbidities excluded; no oral or intravenous antibiotics, systemic immunomodulators, extreme diets, or probiotics 12 wk prior to sample collection	Stool	16S rRNA	No significant difference in alpha diversity Distinct gut microbial communities *Achromobacter*, *Megasphaera*, and *Lachnospiraceae* reported as biomarkers of AA
Rangu et al (2021)	Cross-sectional, n = 82 pediatric (41 AA, 41 HC siblings), USA	Age range = 4−17 y, 73.2% female, 70.7% White/Caucasian; 63.4% SALT <50, 36.6% ≥ SALT 50; siblings aged 4−17 y used as controls; not disclosed: age of disease onset and disease duration	Atopy 26.8% of AA (including eczema, seasonal allergies, asthma, food allergies); no oral antibiotics 6 mo prior to sample collection	Stool	Shotgun metagenomic sequencing	No significant difference in alpha diversity (Shannon index) or beta diversity (Bray−Curtis), small difference in alpha/beta measured by Jaccard distance Decreased abundance of *Ruminococcus bicirculans*
Bain et al (2022)	Cross-sectional, n = 50 stool (41 AA, 19 HCs), n = 57 serum (37 AA, 20 HCs), UK	Stool studies: Mean age: AA 45 y, HC 41 y; AA 95.1% female, HC 94.7% female; 39% SALT <50, 43.9% SALT >50 Serum studies: Mean age: AA 42 y, HC 39 y; AA 83.7% female, HC 80% female; 29.7% SALT <50, 62.1% SALT >50 Not disclosed: age of disease onset and disease duration	Stool studies: comorbid atopy (65.8%), thyroid (19.5%); treatment: none (53.6%), IL steroid (29.3%), DPCP (12.2%), and methotrexate (4.9%) Serum studies: comorbid atopy (56.8%), thyroid (16.2%); treatment: none (56.8%), IL steroid (21.6%), DPCP (18.9%), and methotrexate (2.7%)	Stool Serum blood	16S rRNA, flow cytometry	Reduced evenness (alpha diversity, Shannon index), no significant difference in beta diversity (Bray−Curtis) High SALT associated with changes to beta diversity: enriched *Alistipes*, *Bacteroides*, and *Barnesiella* and reduced *Lachnospiraceae* and *Ruminococcacaee* Increased circulating CCR6+CD4 cells
Brzychcy et al (2022)	Cross-sectional, n = 25 (AA), no control group, Poland	Mean age = 36.8 y, 76% female, 80% SALT <50, 20% ≥ SALT 50; not disclosed: age of disease onset, disease duration	Comorbidities include atopic dermatitis (12%), psoriasis (4%), thyroid (16%), RA (8%), vitiligo (4%), and DM1 (8%); patients excluded if prior systemic immunosuppressants, glucocorticoid therapy or anthralin, signs of infection, or antibiotics (30 d) or probiotics (15 d) prior to sample collection	Stool	16S rRNA	*Lachnoclostridium*, *Bifidobacterium*, *Streptococcus*, and *Eubacterium* as 4 major genera composing AA gut microbiome

(*continued*)

Table 2. Continued

Reference	Study Design	AA Patient Characteristics	Comorbidities, Treatments and Exclusion Criteria	Sampling Method	Identification Method	Reported Changes in AA
Nikoloudaki et al (2024)	Cross-sectional, n = 42 (24 AA, 18 HCs), Italy	Mean age: AA 40 y, HC 45 y; AA 66.7% female, HC 61.1% female; 100% White/Caucasian; mean SALT = 87.46; not disclosed: age of disease onset, disease duration	Comorbid celiac disease (8.3%) and allergic rhinitis (4.2%) in AA group; patients with dermatologic comorbidities excluded; no topicals or immunosuppressants (3 mo), antibiotics (30 d), or probiotics (15 d) prior to sample collection	Stool	16S rRNA	Reduced evenness (Shannon index) and reduced species richness (Chao1 index), no significant difference in beta diversity Microbial biomarkers for AA include Firmicutes, *Lachnospirales*, and *Blautia*
Lee et al (2024)	Cross-sectional, n = 39 (19 AA, 20 HCs), Korea	Mean age: AA 44.6 y, HC 50.5 y; AA 42.1% female, HC 30% female; SALT S1 (limited) 57.9%, SALT S2–S5 42.1%; not disclosed: age of disease onset and disease duration	No reported autoimmune or atopic comorbidities; patients with coexisting scalp dermatoses or other hair loss conditions excluded; no systemic antibiotics, systemic immunomodulators, extreme diets, or probiotics 12 wk prior to sample collection	Stool	16S rRNA	No significant difference in alpha diversity Enriched *Blautia*, *Collinsella*, and *Dorea* and decreased *Bacteroides*

Abbreviations: AA, alopecia areata; AU, alopecia universalis; DM1, diabetes mellitus type 1; DPCP, diphencyprone; FMT, fecal microbiota transplantation; HC, healthy control; IL, intralesional; RA, rheumatoid arthritis; rRNA, ribosomal RNA; SALT, Severity of Alopecia Tool; UK, United Kingdom; USA, United States of America.

in alpha diversity may lead to an inflammatory environment. A link between gut dysregulation and immune-mediated hair loss has been postulated, such as in a recent systematic review and meta-analysis where an association between IBD and AA was proposed (Maghfour et al, 2021). However, other large, population-based studies fail to demonstrate links between IBD and AA and, instead, demonstrate association of AA with age-dependent atopic or autoimmune comorbidities (Chu et al, 2011). Certainly, IBD may be associated with AA, but coexistence of these conditions may be mediated through autoimmune predisposition and not entirely explained by gut dysregulation.

Hair growth is impacted by gut dysbiosis, through mechanisms such as bacterial production of biotin and SCFAs, and vitamin D deficiency. It is therefore proposed that restoration of gut microbiota may lead to hair regrowth by enhancing the absorption and synthesis of nutrients (Carmona-Cruz et al, 2022). This is further bolstered by the observation that serum levels of micronutrients, including vitamin D, zinc, and folate, are lower in patients with AA and that vitamin A levels may modulate AA disease (Thompson et al, 2017). Vitamin D metabolism is influenced by bacteria that express enzymes capable of activating vitamin D (Szaleniec et al, 2018), and vitamin D supplementation changes the composition of gut microbiota in vitamin D–deficient individuals (Schäffler et al, 2018). Disease severity of AA is inversely correlated with levels of vitamin D in adults and children (Daroach et al, 2018; Gade et al, 2018; Unal and Gonulalan, 2018), and there are significant associations between the composition of gut microbiota and vitamin D levels (Yamamoto and Jørgensen, 2019). Exogenous application of vitamin D to T cells and PBMCs causes increased release of IL-10 (an anti-inflammatory cytokine) and decreased release of IFN-γ (Ragab et al, 2016; Sheikh et al, 2018). This suggests vitamin D may exert protective effects in AA by decreasing the release of IFN-γ and maintaining immune privilege at the hair follicle (Lin et al, 2019). The role of vitamin D has been broadly explored in AA, as patients often exhibit low vitamin D levels in samples taken from blood, serum, or tissue (Aksu Cerman et al, 2014; Bakry et al, 2016). High-dose oral calcitriol or paricalcitol effectively treated 3 cases of severe pediatric alopecia (alopecia universalis and AA) (Papadimitriou et al, 2021), and intralesional vitamin D administration led to hair regrowth for localized patchy alopecia in a randomized controlled trial of 60 adult patients (Rashad et al, 2022). A small pilot study of 22 patients with AA found that administration of calcipotriol lotion for 3 months led to increased serum vitamin D levels and response to treatment (hair regrowth) in patients with low vitamin D levels at baseline (Narang et al, 2017). Topical calcipotriol (0.005% ointment) led to a small but statistically significant reduction in Severity of Alopecia Tool (SALT) score when used alone (SALT score of 7.22 at baseline and of 2.98 at 24 weeks) or in combination with topical corticosteroids (SALT score of 6.05 at baseline and of 2.66 at 24 weeks) in a small, unblinded study of patients with AA, affecting <50% of the scalp (Alam et al, 2019). However, the clinical significance of this finding requires further

interrogation in larger studies with blinding of participants and researchers.

Given the composition of gut microbiota is distinct in patients with AA, it is plausible that targeting microbial changes may lead to therapeutic benefit. A case report in 2011 described the resolution of AA after eradication of *Helicobacter pylori* infection with amoxicillin, clarithromycin, and omeprazole for 2 weeks in a man aged 43 years (Campuzano-Maya, 2011). However, there are also reports of relapse of AA after longer-term rifampicin therapy (McMillen and Duvic, 2001) and other antitubercular therapies (Tella et al, 2014). Sulfasalazine, a common disease-modifying antirheumatic drug, is a combination of salicylate (5-aminosalicylic acid [5-ASA]) and the antibacterial agent sulfapyridine (Karagozian and Burakoff, 2007) and is used to treat chronic inflammatory conditions, such as rheumatoid arthritis or ulcerative colitis. Although sulfasalazine is not standard of treatment for AA, reports of its use in AA are mechanistically interesting because it modulates gut microbiota through its antibacterial properties (Yang et al, 2016). There are reports of >50% hair regrowth in patients with refractory AA (Bakar and Gurbuz, 2007; Rashidi and Mahd, 2008) and 100% maintenance of areas of regrowth with sulfasalazine therapy (Bakar and Gurbuz, 2007). However, the use of mesalazine, a 5-ASA derivative lacking the antibacterial component sulfapyridine (Karagozian and Burakoff, 2007), also showed satisfactory hair growth response in 5 pediatric patients when combined with other therapies (corticosteroids, minoxidil) (Kiszewski et al, 2018), suggesting that the anti-inflammatory activity of sulfasalazine rather than the antibacterial action may be sufficient to allow hair regrowth.

FUTURE DIRECTIONS

The studies highlighted in this review underscore the growing evidence for changes in microbial populations in AA. Moreover, findings in a small subset of patients show correlation between microbial dysbiosis and increased expression of proapoptotic and inflammatory markers and perifollicular inflammation in patients with AA (Rinaldi et al, 2022a; Pinto et al, 2020a). Yet, the causal link between microbial dysbiosis and the pathogenesis of AA requires further investigation, with larger and more diverse patient cohorts and under controlled conditions. Indeed, it is not unexpected that bacterial populations exhibit differences in composition between hair-bearing regions of the scalp and nonhair-bearing (alopecia) lesions. It is well-established that the cutaneous microbiome varies on the basis of anatomic location and the local microarchitectural changes in these areas (pH, humidity, presence of sebaceous glands). At hair-bearing sites, sebum adheres predominantly to the hair shaft. Within alopecia lesions, there is increased excretion of sebum directly onto the scalp skin itself, which directly modulates the physiologic properties of the skin and likely contributes to the observed differences in microbial populations at hair-bearing versus nonhair-bearing sites. Studies investigating differences between microbial populations within the hair follicles (eg, samples obtained through hair-pull test or biopsy) may prove more relevant to the pathophysiology of AA than changes observed on the surface of the scalp. To our knowledge, this problem has not been addressed in the current literature. Additional studies may also benefit from inclusion of nonlesional or perilesional samples from hair-bearing regions of patients with AA (when available). These samples would provide valuable internal controls and important areas to compare bacterial composition in architecturally distinct areas on the same patient. In addition, we were unable to uncover any studies that characterize changes in the microbiome within the pilosebaceous unit during the normal hair cycle. This may be of particular relevance, given changes in the tight junction function during different phases of the hair cycle, with enhanced penetration of exogenous particles during anagen phase (Vogt et al, 2020). Longitudinal studies examining the composition of bacterial populations within the gut and at sites of hair regrowth in patients with AA would also enhance our current understanding of bacterial dysbiosis in AA. There is increasing evidence for the role of probiotics in skin health (Markowiak and Śliżewska, 2017), as this leads to increased levels of beneficial bacteria, which reduce inflammation and regulate immune function, yet no studies have examined the role of probiotics in AA. Taken together, we acknowledge that sufficient data exist to support changes in bacterial composition in patients with AA compared to healthy controls; however, further studies are required to delineate the directionality of the relationship between bacterial dysbiosis and inflammation of AA and, importantly, whether these changes may have implications for therapy.

CONCLUSION

Cutaneous and gut dysbiosis is emerging as a complex factor in the disease pathogenesis of AA. Similar to patients with other inflammatory skin diseases (ie, acne vulgaris and AD), patients with AA show overgrowth of *C acnes* and *Corynebacterium* species and decreased proportions of the coagulase-negative *S epidermidis* and *S caprae*. Alterations in cutaneous microbiota may modulate the local immune system by recruiting immune cells and stimulating an inflammatory cascade, although the precise mechanisms through which these changes contribute to the pathogenesis of AA remain unclear. In addition, patients with AA exhibit distinct composition of gut microbiota, with decreased abundance of Bacteroidetes, *Lachnospiraceae*, and *Ruminococcaceae*. These bacteria are known to produce SCFAs, which are important regulators of intestinal permeability, systemic inflammation, and serum vitamin D levels. Increased understanding of dysbiosis of the skin, hair follicle, and gut in AA may open the possibility for new therapeutic strategies and treatment adjuncts.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: NEB, MLR; Supervision: MLR; Visualization: NEB; Writing - Original Draft Preparation: NEB; Writing - Review and Editing: NEB, MLR

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) OR LARGE LANGUAGE MODELS (LLMS)

The authors did not use AI/LLM in any part of the research process and/or manuscript preparation.

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