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Alopecia Areata: Advances in Etiopathogenesis, Clinical Manifestations, and Evolving Diagnostic Strategies

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ABSTRACT

Background: Alopecia areata (AA) is a chronic, immune-mediated disorder of the hair follicle characterized by nonscarring hair loss with a highly variable clinical course. It represents one of the most common autoimmune conditions affecting the skin, with a lifetime risk of approximately 1–2%. The disease is multifactorial, arising from complex interactions among genetic predisposition, immune dysregulation, cytokine and chemokine signaling, and environmental influences. Beyond hair loss, AA carries profound psychosocial consequences and is associated with multiple systemic and autoimmune comorbidities, highlighting its significance as a systemic disease rather than merely a dermatological condition. **Aim:** This review aims to provide an updated and comprehensive overview of alopecia areata, focusing on epidemiology, advances in etiopathogenesis—including genetic factors, immune pathways, chemokine signaling, and novel mechanisms such as autophagy and microbiome involvement—as well as clinical spectrum, comorbidities, diagnostic strategies, and scoring systems. Emphasis is placed on bridging current understanding of molecular pathways with clinical manifestations, thereby facilitating early diagnosis, risk stratification, and precision-based management. **Conclusion:** Recent advances in immunologic and genetic research have significantly expanded the understanding of alopecia areata as a complex systemic autoimmune disease. Aberrant immune activation targeting the hair follicle's immune privilege, mediated by interferon-γ, interleukin signaling, and chemokines such as CXCL9 and CXCL10, plays a pivotal role in disease initiation and progression. Genetic susceptibility loci, environmental triggers, and epigenetic regulation further modulate disease risk and expression. Clinically, AA exhibits a broad spectrum ranging from patchy hair loss to alopecia totalis and universalis, often accompanied by nail changes and associations with thyroid disease, psychiatric conditions, and metabolic disorders. Diagnosis remains primarily clinical but is increasingly supported by dermoscopy, scalp imaging, and molecular tests, with severity and progression assessed by standardized scoring tools such as the SALT and AAPS indices. By integrating evolving insights into pathogenesis with detailed clinical evaluation, clinicians can improve prognostication, tailor therapies, and address the psychosocial burden borne by patients. Continued interdisciplinary research is essential to translate mechanistic discoveries into novel therapeutic strategies for this disabling yet potentially reversible condition.

Keywords*: Alopecia Areata, Etiopathogenesis, Diagnostic Strategies*

Introduction

Alopecia areata (AA) is a chronic, immune-mediated disorder that targets the hair follicle, leading to nonscarring hair loss. It affects both sexes and all age groups, with onset most commonly in childhood and young adulthood. The condition exhibits a highly unpredictable course, ranging from transient

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patchy alopecia to complete loss of scalp and body hair, known as alopecia totalis and universalis. Although the hair follicle itself remains intact and retains the potential for regrowth, disease flares and relapses are frequent, making AA a condition with significant clinical, psychological, and social implications [1].

The global prevalence of AA is estimated at 0.1–0.2%, with a lifetime risk of 1–2%, positioning it among the most common autoimmune diseases. The burden extends beyond cosmetic concerns; patients often experience stigmatization, impaired quality of life, anxiety, depression, and difficulties in interpersonal relationships. Furthermore, an increasing body of evidence highlights systemic associations between AA and comorbidities, including autoimmune thyroid disease, vitiligo, atopic dermatitis, cardiovascular disorders, and insulin resistance [2]. This suggests that AA represents not only a localized immune dysregulation but also a systemic immunologic disorder.

The pathogenesis of AA is multifactorial, encompassing genetic predisposition, immune-mediated follicular attack, environmental triggers, and more recently, epigenetic and microbiome-related influences. Central to disease initiation is the collapse of immune privilege at the hair follicle, accompanied by infiltration of autoreactive CD8+ T cells and upregulation of cytokines such as interferon-γ and interleukin-15. Chemokines, particularly CXCL9 and CXCL10, orchestrate immune cell recruitment, perpetuating follicular damage. Recent studies also implicate dysregulated autophagy and alterations in the skin and gut microbiome in disease susceptibility and chronicity [3].

Despite these advances, critical research gaps remain. The heterogeneity of AA poses challenges in predicting disease onset, severity, and long-term outcomes. Current diagnostic strategies rely largely on clinical and dermoscopic evaluation, with limited integration of molecular or genetic tools in daily practice. Moreover, existing severity scoring systems, while helpful, do not fully capture disease burden or predict treatment response. Bridging the gap between molecular discoveries and clinical practice is essential for developing personalized, evidence-based management strategies.

The aim of this review is to provide a comprehensive synthesis of current knowledge on alopecia areata, covering epidemiology, etiopathogenesis—including genetics, immune pathways, and novel mechanisms—clinical spectrum, associated comorbidities, diagnostic modalities, and scoring tools. By linking pathophysiologic mechanisms with clinical features and diagnostic approaches, this review seeks to enhance understanding of AA as a systemic disorder and guide clinicians and researchers toward improved patient outcomes [4].

Epidemiology

Alopecia areata (AA) is among the most common autoimmune diseases worldwide, with an estimated lifetime risk of 1–2%. The point prevalence in the general population ranges between 0.1% and 0.2%, though variation exists due to geographic, ethnic, and methodological factors in epidemiologic surveys

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[5]. It is estimated that AA accounts for up to 2% of dermatology outpatient visits globally, underscoring its clinical importance and significant healthcare burden [6].

The disease has no gender predilection, affecting males and females almost equally. However, subtle differences in clinical expression have been noted, with some studies suggesting that severe subtypes such as alopecia totalis and universalis are more frequent in males, whereas females may present earlier with patchy hair loss [7]. AA occurs in all age groups, but onset is most common in the first three decades of life, with approximately 60% of cases manifesting before the age of 20 years. Childhood-onset AA often indicates a more severe and persistent course, highlighting the importance of early recognition and monitoring [8].

Epidemiologic trends also vary with ethnicity and geography. For instance, studies in the United States and Europe demonstrate prevalence rates close to 2%, while certain Asian and Middle Eastern populations report slightly higher or lower figures depending on genetic background and environmental influences [9]. Research has shown that populations with higher frequencies of autoimmune conditions, such as vitiligo and thyroid disease, also exhibit higher rates of AA, supporting shared pathogenetic mechanisms [10].

Beyond prevalence, the socioeconomic burden of AA is considerable. Direct healthcare costs include consultations, diagnostic evaluations, and therapeutic interventions, while indirect costs relate to work absenteeism, decreased productivity, and psychosocial support services. Patients with AA frequently report diminished quality of life comparable to that observed in chronic skin diseases such as psoriasis and atopic dermatitis. Stigmatization, low self-esteem, and psychiatric morbidity including anxiety and depression significantly amplify the overall disease burden, making AA both a medical and social health concern [11].

Longitudinal cohort studies also indicate that AA follows a relapsing-remitting course, with spontaneous remission occurring in up to 30–50% of patients within one year of onset. However, relapse is common, and severe forms such as alopecia totalis and universalis often demonstrate chronic persistence. Epidemiologic evidence underscores the unpredictability of disease outcomes and the difficulty in establishing reliable prognostic indicators, further emphasizing the need for refined diagnostic and scoring systems [12].

Etiopathology

1. Genetic Factors

Genetic predisposition is a key determinant in the development of alopecia areata (AA), as evidenced by familial aggregation and twin studies. Approximately 10–20% of AA patients report a positive

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family history, with higher concordance rates among monozygotic twins compared to dizygotic twins, suggesting a strong heritable component [13]. These findings indicate that genetic susceptibility is a cornerstone of disease initiation, although environmental and immunological triggers are required for clinical manifestation.

Genome-wide association studies (GWAS) have identified multiple susceptibility loci for AA. Notably, regions within the major histocompatibility complex (MHC), particularly HLA-DR and HLA-DQ alleles, have been consistently implicated in disease susceptibility [14]. These loci underscore the central role of antigen presentation in the autoimmune response against hair follicles. Beyond the MHC, additional risk loci include genes involved in immune regulation such as IL2RA, IL2/IL21, CTLA4, and genes related to natural killer (NK) cell function, including ULBP3 and ULBP6 [15]. The identification of these loci highlights the convergence of adaptive and innate immune dysregulation in AA.

Several studies have revealed ethnic differences in genetic associations, reflecting population-specific risk profiles. For example, in Caucasian populations, HLA-DRB1*1104 and HLA-DQB1*0301 are strongly associated with AA, whereas in East Asian populations, HLA-DRB1*1501 and HLA-DQB1*0503 appear more relevant [16]. These variations underscore the importance of considering genetic heterogeneity when studying disease mechanisms and tailoring therapeutic interventions across diverse populations.

Genetics also play a role in modulating disease phenotype and severity. Certain alleles, such as HLA-DRB1*1104, have been linked with severe and persistent forms including alopecia totalis and universalis, while others correlate with patchy or transient disease [17]. Furthermore, genetic susceptibility overlaps significantly with other autoimmune disorders, explaining the frequent co-occurrence of AA with conditions such as type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, and autoimmune thyroiditis. This overlap reinforces the concept of AA as part of a broader autoimmune diathesis [18].

Emerging research into epigenetics is further expanding the genetic landscape of AA. While heritable DNA sequence variations are important, environmental exposures and epigenetic modifications, including DNA methylation and histone acetylation, can modulate gene expression and immune responses. This gene-environment interaction helps explain variability in disease onset, course, and treatment response among genetically predisposed individuals [19].

2. Immunity, Cytokines and Signaling Pathways

The immunopathogenesis of alopecia areata (AA) is primarily driven by a collapse of the hair follicle's immune privilege, leading to an aberrant immune attack on anagen hair follicles. In healthy conditions, the lower hair follicle bulb is relatively protected from immune surveillance due to low expression of

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MHC class I molecules and local immunosuppressive cytokines such as TGF-β and α-MSH. In AA, this immune privilege collapses, resulting in upregulation of MHC class I and II molecules and exposure of autoantigens that activate autoreactive immune cells [20].

Cytotoxic CD8+ NKG2D+ T cells are central to disease pathogenesis. These cells infiltrate the peribulbar region, forming the characteristic "swarm of bees" histological pattern. Activated CD8+ T cells release interferon-gamma (IFN-γ), which amplifies local inflammation and promotes further antigen presentation by follicular keratinocytes. IFN-γ also induces the expression of interleukin-15 (IL-15), a cytokine critical for T-cell survival and proliferation. The IL-15/IL-15R pathway, together with Janus kinase (JAK)-STAT signaling, creates a self-sustaining inflammatory loop that perpetuates follicular damage [21].

Regulatory T cells (Tregs), which normally suppress autoreactive responses, appear numerically or functionally deficient in AA, further contributing to unchecked immune activation. Additionally, altered activity of natural killer (NK) cells has been observed, particularly involving stress ligands such as MICA and ULBP proteins that interact with NKG2D receptors. These findings highlight a complex interplay of adaptive and innate immunity in AA [22].

Chemokines, particularly CXCL9 and CXCL10, play crucial roles in recruiting pathogenic T cells to the hair follicle. Both chemokines are strongly upregulated in AA lesions under the influence of IFN-γ. CXCL9 and CXCL10 act via the CXCR3 receptor, promoting the migration and retention of Th1 cells and cytotoxic CD8+ T cells at the follicular site. Elevated CXCL9 and CXCL10 expression correlates with disease activity and severity, making them potential biomarkers and therapeutic targets. Inhibition of the CXCL10–CXCR3 axis has demonstrated promising results in experimental models of AA, supporting the rationale for chemokine-targeted therapies [23].

The JAK-STAT pathway represents a pivotal signaling axis in AA. Cytokines such as IFN-γ and IL-15 exert their effects by activating JAK kinases, which in turn phosphorylate STAT transcription factors, leading to expression of pro-inflammatory genes. This discovery has revolutionized therapeutic approaches to AA, with JAK inhibitors (e.g., tofacitinib, ruxolitinib, baricitinib) showing significant efficacy in clinical trials. These agents disrupt the pathogenic feedback loop of cytokine signaling, reducing inflammation and enabling hair regrowth in affected patients [24].

Taken together, AA is now recognized as a T cell–mediated autoimmune disease orchestrated by IFN-γ, IL-15, chemokines such as CXCL9/CXCL10, and JAK-STAT signaling. This immunologic framework not only explains the follicular damage seen in AA but also provides a strong foundation for novel immunomodulatory therapies, some of which are already entering routine clinical practice [25].

3. Environmental Factors

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While genetic susceptibility and immune dysregulation form the foundation of alopecia areata (AA), environmental factors serve as important triggers for disease initiation and exacerbation. The interplay between genetic predisposition and environmental exposures explains the heterogeneity of disease expression among patients with similar genetic risk. Numerous external stimuli—including infections, stress, medications, and lifestyle factors—have been implicated in precipitating AA episodes [26].

Psychological stress is among the most widely recognized triggers. Stress can disrupt neuroendocrine-immune homeostasis by increasing cortisol release and altering hypothalamic–pituitary–adrenal (HPA) axis activity. Stress mediators such as substance P and corticotropin-releasing hormone promote mast cell degranulation and cytokine release within the skin, thereby facilitating hair follicle immune privilege collapse. Patients frequently report stressful life events preceding disease onset or relapse, although causality remains complex due to the bidirectional relationship between AA and psychological distress [27].

Infections have also been proposed as environmental contributors. Viral and bacterial pathogens may trigger molecular mimicry or bystander activation, leading to autoreactive T cell responses. Associations have been reported between AA and viral infections such as cytomegalovirus, Epstein-Barr virus, and more recently, SARS-CoV-2. Post-COVID-19 cases of AA onset or flare have been increasingly documented, possibly due to immune hyperactivation, elevated interferon responses, or vaccination-related immune modulation [28]. However, the evidence remains inconclusive, and infections may act as nonspecific immune triggers rather than direct etiologic agents.

Medications are another important category of environmental factors. Reports suggest that biologic agents such as immune checkpoint inhibitors, used in cancer immunotherapy, can precipitate AA as part of an immune-related adverse event profile. Similarly, TNF-α inhibitors, interferons, and other immunomodulatory drugs have been associated with disease onset in susceptible individuals. These observations support the concept that immune system perturbation, regardless of cause, may unmask latent susceptibility to AA [29].

Lifestyle and dietary factors may indirectly contribute by modulating immune function and systemic inflammation. Low vitamin D levels, micronutrient deficiencies (zinc, iron), smoking, and metabolic disturbances have all been associated with increased AA risk or severity. Furthermore, sleep disruption and circadian rhythm alterations may impair follicular regeneration and immune regulation, adding to the multifactorial burden of environmental stressors [30].

Overall, environmental factors serve as modulators that interact with underlying genetic and immunologic predispositions to shape disease onset, progression, and recurrence. Identifying and managing these factors—such as reducing stress, correcting nutritional deficiencies, and monitoring drug exposures—may provide supportive strategies to complement immunologic and targeted therapies in AA [31].

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4. Other Etiological Factors

Epigenetic Factors

Epigenetics provides an additional layer of complexity in the etiopathogenesis of alopecia areata (AA), explaining how environmental influences interact with genetic predisposition to alter immune responses. Epigenetic mechanisms such as DNA methylation, histone modification, and non-coding RNAs regulate gene expression without changing the underlying DNA sequence. Studies have demonstrated altered DNA methylation patterns in AA patients, particularly in immune-related genes such as HLA and interleukin signaling pathways [32]. Dysregulation of microRNAs (miRNAs), including miR-155 and miR-31, has also been implicated in immune activation and follicular damage. Epigenetic changes may not only trigger disease onset but also influence chronicity and treatment resistance, making them potential therapeutic targets [33].

Autophagy

Autophagy, a cellular degradation and recycling process essential for homeostasis, has recently been linked to AA. Impaired autophagy may disturb hair follicle immune privilege and antigen presentation. Key autophagy-related genes such as ATG5 and ATG7 have shown altered expression in AA, suggesting defective clearance of damaged proteins and organelles, which may enhance immune recognition of follicular antigens [34]. Furthermore, cross-talk between autophagy and the JAK-STAT pathway highlights autophagy as both a regulator and a consequence of immune activation in AA. Emerging data suggest that modulating autophagy may restore immune tolerance at the follicular level, opening new therapeutic avenues [35].

Microbiome

The role of the microbiome—both cutaneous and gut—in AA pathogenesis is gaining increasing attention. The scalp microbiome in AA patients exhibits shifts in bacterial composition, with overrepresentation of pro-inflammatory species such as *Staphylococcus aureus* and depletion of protective commensals. These microbial imbalances may enhance local immune activation, follicular inflammation, and barrier dysfunction [36]. Beyond the scalp, gut dysbiosis has been reported in AA, with reduced diversity and altered abundance of species associated with immune regulation. The gut-skin axis suggests that intestinal dysbiosis may prime systemic immune dysregulation, contributing to follicular autoimmunity [37]. Probiotic supplementation and dietary interventions are being investigated as adjunctive measures to restore microbiome balance and potentially ameliorate AA severity.

Taken together, epigenetic regulation, autophagy dysfunction, and microbiome alterations represent emerging etiological dimensions of AA. These mechanisms extend beyond classical genetic and immune paradigms, offering novel insights into disease susceptibility and chronicity. Importantly, they

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underscore the potential of personalized approaches that combine immunomodulation with strategies targeting epigenetic machinery, cellular homeostasis, and microbial ecosystems [38].

Clinical Features

Alopecia areata (AA) presents with a wide clinical spectrum ranging from localized, patchy hair loss to complete loss of scalp and body hair. The hallmark feature is nonscarring alopecia, where the follicular openings remain preserved, allowing the potential for regrowth. The disease course is unpredictable, with alternating phases of hair loss and regrowth, often influenced by underlying immunologic activity [39].

Hair Loss

The most common clinical presentation is one or more well-demarcated, round or oval patches of hair loss on the scalp. Lesions are usually smooth, with normal-appearing skin devoid of scaling or erythema, distinguishing AA from inflammatory alopecias such as tinea capitis or discoid lupus erythematosus. Patchy AA may remain localized, but in some cases, it progresses to alopecia totalis (complete scalp hair loss) or alopecia universalis (total scalp and body hair loss), representing the most severe phenotypes [40]. Ophiasis, a less common variant, manifests as band-like hair loss along the temporal and occipital scalp, often associated with chronicity and poor prognosis. Diffuse AA, though rare, presents with widespread thinning resembling telogen effluvium, complicating clinical recognition [41].

Hypopigmented Hair Regrowth in AA

One of the distinctive features of AA is the regrowth of hypopigmented or white hairs in previously affected areas. This phenomenon reflects selective immune targeting of pigmented hair follicles, sparing non-pigmented follicles during disease activity. Hypopigmented regrowth may persist temporarily or indefinitely, contributing to cosmetic concerns, particularly in darker-haired individuals. Over time, normal pigmentation often returns, though recurrent episodes may again preferentially affect pigmented follicles [42].

Nail Involvement

Nail abnormalities are observed in approximately 10–20% of patients with AA, with higher prevalence in severe subtypes. The most characteristic nail finding is fine stippled pitting, often described as “sandpaper nails.” Other manifestations include trachyonychia, onychorrhexis, onycholysis, Beau’s lines, and red-spotted lunulae. Nail involvement is clinically significant, as it often correlates with chronic and refractory disease, serving as a negative prognostic indicator. Children with AA and nail changes tend to have more severe forms, underscoring the importance of nail examination in clinical evaluation [43].

Course and Prognosis

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The clinical course of AA is notoriously unpredictable. Spontaneous remission occurs in up to 30–50% of patients within one year, particularly in those with limited patchy involvement. However, recurrence is common, and some patients experience a relapsing-remitting pattern throughout life. Poor prognostic indicators include early age of onset, ophiasis pattern, nail involvement, family history of autoimmune disease, and progression to alopecia totalis or universalis. Long-term outcomes remain difficult to predict, complicating counseling and therapeutic decision-making [44].

Associated Comorbidities

Alopecia areata (AA) is increasingly recognized as a systemic autoimmune disease with multiple comorbid conditions rather than merely a localized hair disorder. The association with other systemic diseases underscores shared immunogenetic pathways, especially involving autoimmunity, inflammation, and metabolic dysregulation. Identifying these comorbidities is essential for holistic patient care, as they may influence disease prognosis, therapeutic choices, and quality of life [45].

Thyroid Disorders

Autoimmune thyroid disease is the most consistently reported comorbidity in AA. Both Hashimoto's thyroiditis and Graves' disease occur with increased frequency, with prevalence estimates ranging from 8% to 28% depending on population studied. Thyroid autoantibodies, including anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin antibodies, are commonly detected even in clinically euthyroid patients. Routine screening for thyroid dysfunction is recommended, particularly in children and patients with extensive or chronic AA [46].

Mental Disorders

The psychosocial burden of AA is profound, and psychiatric comorbidities such as depression, anxiety, and social phobia are highly prevalent. Studies show that up to 40% of AA patients experience clinically significant psychiatric symptoms. The relationship is bidirectional: psychological stress can exacerbate AA, while AA-induced cosmetic disfigurement worsens mental health outcomes. Importantly, pediatric and adolescent patients are particularly vulnerable, with higher rates of bullying, stigmatization, and long-term psychological sequelae [47].

Skin Inflammatory Diseases

AA frequently coexists with other inflammatory skin disorders, particularly atopic dermatitis and vitiligo. Both conditions share immune mechanisms involving Th1/Th2 imbalance and autoimmunity against melanocytes or barrier structures. Vitiligo and AA often coexist within the same patient, reflecting common pathways of immune privilege collapse. Psoriasis has also been linked with AA, though the relationship appears less consistent. The coexistence of these dermatologic disorders complicates clinical management and may alter therapeutic responses [48].

Cardiovascular Diseases

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Chronic systemic inflammation in AA may extend beyond the skin to cardiovascular risk. Several epidemiologic studies suggest that AA patients have an elevated risk of hypertension, dyslipidemia, and ischemic heart disease. Increased inflammatory cytokines and immune activation may promote endothelial dysfunction and atherosclerosis, paralleling mechanisms seen in psoriasis. While causality is debated, cardiovascular screening is advisable in patients with extensive or long-standing AA [49].

Insulin Resistance and Metabolic Disorders

Emerging evidence suggests that AA is associated with insulin resistance and metabolic syndrome. Studies have demonstrated higher rates of obesity, impaired glucose tolerance, and dyslipidemia in AA cohorts compared to controls. Chronic low-grade inflammation and cytokine dysregulation may impair insulin sensitivity, creating a pathogenic link. Recognizing and addressing metabolic dysfunction in AA is essential for comprehensive care, particularly in younger patients with severe or recurrent disease [50].

Autoimmune Comorbidities

AA exhibits strong overlap with systemic autoimmune conditions. Type 1 diabetes, systemic lupus erythematosus, celiac disease, rheumatoid arthritis, and multiple sclerosis occur with increased frequency among AA patients. Family clustering of autoimmune diseases further supports the concept of a shared autoimmune diathesis. The coexistence of multiple autoimmune disorders often signals a more severe or refractory AA course, necessitating careful long-term monitoring [51].

Other Inflammatory Diseases

Beyond classical autoimmune conditions, AA has also been linked to inflammatory bowel disease (ulcerative colitis and Crohn's disease), allergic rhinitis, and asthma. These associations reflect broader systemic immune dysregulation involving Th1, Th2, and Th17 pathways. Although less consistently reported, these conditions reinforce the need for interdisciplinary care in AA patients, particularly when symptoms extend beyond dermatologic manifestations [52].

Diagnosis

The diagnosis of alopecia areata (AA) is primarily clinical, supported by characteristic patterns of hair loss and dermoscopic features. Ancillary investigations such as histopathology, imaging techniques, and laboratory tests are reserved for atypical presentations, prognostic evaluation, or exclusion of differential diagnoses. Standardized scoring systems aid in disease monitoring and clinical trial outcomes [53].

1. Clinical Picture of Hair Loss

AA typically presents as well-circumscribed, round or oval patches of hair loss with smooth, normal-appearing skin. Follicular ostia remain preserved, differentiating AA from scarring alopecias. In diffuse variants, hair thinning is widespread, mimicking telogen effluvium, while ophiasis manifests as band-like alopecia along the temporal and occipital scalp. Complete scalp or body hair loss (alopecia

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totalis/universalis) reflects severe disease. Recognition of these characteristic clinical morphologies forms the cornerstone of diagnosis [54].

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2. Hair Pulling Test

The hair pull test is a simple bedside maneuver to assess disease activity. A positive test, indicated by easy extraction of multiple telogen or dystrophic anagen hairs from the periphery of alopecic patches, suggests active disease. Repeated testing over time provides insights into disease progression or remission. Although not specific to AA, its utility lies in gauging current disease activity and informing treatment decisions [55].

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3. Trichoscopy

Dermoscopy (trichoscopy) has become an indispensable non-invasive diagnostic tool for AA. Characteristic features include:

- **Yellow dots** – representing dilated follicular infundibula filled with keratin and sebum, seen in both active and inactive disease.
- **Black dots** – pigmented broken hairs at the follicular opening, indicative of active disease.
- **Exclamation mark hairs** – pathognomonic short hairs tapered proximally, reflecting weakened shafts near inflamed follicles.
- **Broken hairs** – irregular short hairs suggestive of ongoing follicular damage.
- **Honeycomb pigment pattern** – background pigmentation reflecting chronic scalp exposure.
- **Tapered hairs** – regrowing hairs with proximal narrowing, indicating early recovery [56].

Trichoscopy not only facilitates diagnosis but also helps distinguish AA from mimickers such as trichotillomania, tinea capitis, or androgenetic alopecia.

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4. Biopsy

Scalp biopsy is indicated in cases of diagnostic uncertainty, especially when differentiating AA from scarring alopecias. Histology demonstrates peribulbar lymphocytic infiltrates around anagen hair follicles—the "swarm of bees" appearance—along with miniaturization and increased catagen/telogen follicles. Chronic lesions may show decreased follicular density with follicular stelae but without scarring. Biopsy findings provide definitive confirmation when clinical and dermoscopic findings are equivocal [57].

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5. Scalp Imaging Techniques

Novel imaging modalities, including optical coherence tomography, reflectance confocal microscopy, and ultrasound biomicroscopy, are being explored as non-invasive diagnostic aids. These techniques

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enable visualization of follicular architecture, inflammatory infiltrates, and hair shaft abnormalities in real-time. Although currently limited to research settings, they hold promise for early diagnosis, disease monitoring, and therapeutic evaluation [58].

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6. Laboratory Tests

Routine laboratory testing is not necessary for all AA patients but may be warranted in cases of severe, recurrent, or atypical disease. Screening includes thyroid function tests and thyroid autoantibodies, particularly in children. Autoimmune panels may be indicated if systemic disease is suspected. Genetic testing is not yet standard but may gain relevance as precision medicine evolves [59].

Scoring of AA

Standardized scoring systems provide objective measures of disease severity and treatment outcomes.

- **Severity of Alopecia Tool (SALT):** Quantifies percentage scalp hair loss by dividing the scalp into quadrants, widely used in clinical trials and practice.
- **Scoring of the Upper Face and Beard Area:** Extensions of SALT to include eyebrows, eyelashes, and beard involvement, improving assessment of visible disease burden.
- **Alopecia Areata Investigator Global Assessment (AA-IGA):** Provides categorical ratings of disease severity, often used in therapeutic studies.
- **Alopecia Areata Predictive Score (AAPS):** Predicts prognosis based on demographic, clinical, and trichoscopic features.
- **Alopecia Areata Progression Index (AAPI):** A dynamic scoring system capturing disease activity and risk of progression [60].

The integration of these tools standardizes outcome reporting and facilitates comparison across studies, though refinement is still needed to capture psychosocial burden.

Differential Diagnosis

Differentiating alopecia areata (AA) from other causes of hair loss is essential to avoid misdiagnosis and inappropriate management. The nonscarring nature of AA, coupled with characteristic dermoscopic and histopathological findings, guides clinicians in distinguishing it from other alopecias. Nevertheless, overlap in clinical features often complicates the diagnostic process [61].

The most important differential is **trichotillomania**, a psychogenic disorder characterized by compulsive hair pulling. Clinically, trichotillomania presents with irregular patches of hair loss containing hairs of varying lengths and broken shafts, often in bizarre geometric patterns. Unlike AA, trichotillomania lacks smooth, completely bald patches. Trichoscopy shows coiled hairs, flame hairs, and V-sign broken hairs rather than exclamation mark hairs or yellow dots. Histology reveals traumatized follicles without the lymphocytic infiltrates typical of AA [62].

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Tinea capitis is another key consideration, particularly in children. It often presents with patchy alopecia accompanied by erythema, scaling, pustules, or kerion formation. Lymphadenopathy may also be present. Trichoscopy reveals comma hairs and corkscrew hairs, while fungal culture or KOH examination confirms the diagnosis. Unlike AA, tinea capitis is infectious and requires antifungal therapy [63].

Androgenetic alopecia (AGA), the most common form of hair loss, may mimic diffuse or patchy AA. AGA presents with gradual thinning, particularly in androgen-dependent regions, without sharply demarcated patches. Trichoscopy in AGA reveals hair shaft miniaturization with increased hair diameter variability and perifollicular pigmentation (peripilar sign). In contrast, AA demonstrates sudden-onset, well-circumscribed patches and hallmark features such as exclamation mark hairs and yellow dots [64].

Telogen effluvium (TE) is a diffuse form of hair shedding that may resemble diffuse AA. TE typically follows systemic stressors such as illness, surgery, or postpartum state and presents with generalized hair thinning. The hair pull test in TE is usually positive across the entire scalp, whereas in AA it is localized to the periphery of patches. Histology of TE shows an increased proportion of telogen hairs without inflammatory infiltrates [65].

Other rare differentials include **discoid lupus erythematosus (DLE)**, **lichen planopilaris (LPP)**, and other scarring alopecias. These conditions can occasionally mimic AA in early stages but typically progress to permanent hair loss due to follicular destruction. Distinguishing features include perifollicular erythema, scaling, and eventual loss of follicular ostia on examination, with histopathology confirming interface dermatitis and fibrosis [66].

In summary, careful evaluation of clinical morphology, trichoscopy, and histology, supplemented by microbiological or laboratory investigations where appropriate, is essential in distinguishing AA from other causes of alopecia. Accurate diagnosis ensures timely initiation of appropriate therapy and prevents unnecessary interventions [67].

Conclusion

Alopecia areata (AA) is a multifactorial autoimmune disease characterized by complex interactions between genetic predisposition, immune dysregulation, environmental influences, and emerging mechanisms such as epigenetic modifications, autophagy dysfunction, and microbiome alterations. While it manifests primarily as nonscarring hair loss, AA carries profound psychological, social, and systemic implications, underscoring its role as a disease that extends beyond the skin.

Recent advances in molecular immunology have clarified the pivotal role of CD8+ T cells, interferon-γ, IL-15, chemokines such as CXCL9 and CXCL10, and the JAK-STAT signaling pathway in driving follicular autoimmunity. These insights have not only refined disease understanding but also

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revolutionized therapeutic strategies, with JAK inhibitors and targeted biologics offering promising outcomes for patients with refractory disease.

Clinically, AA exhibits a highly variable course, ranging from small, self-limited patches of alopecia to severe, chronic forms such as alopecia totalis and universalis. Prognostic indicators including early age of onset, nail involvement, ophiasis pattern, and associated autoimmune comorbidities remain essential in predicting disease course. Comorbid associations with thyroid disease, psychiatric disorders, cardiovascular risk, and systemic autoimmune conditions highlight the importance of multidisciplinary care.

Diagnosis is primarily clinical, enhanced by trichoscopy, scalp biopsy, and increasingly advanced imaging modalities. Standardized scoring tools such as SALT, AA-IGA, AAPS, and AAPI allow for objective assessment of disease severity and therapeutic response, though ongoing refinement is needed to capture psychosocial burden and quality-of-life impact.

Despite these advances, significant research gaps remain. The unpredictable natural history, variability in treatment response, and incomplete understanding of environmental and epigenetic modulators continue to challenge clinicians and researchers. Future directions should focus on precision medicine approaches that integrate genetic, immunologic, and microbiome profiling with clinical features to enable personalized therapy and prognostication.

In conclusion, alopecia areata is no longer regarded as a simple hair disorder but as a systemic autoimmune disease with profound dermatologic and psychosocial consequences. Bridging the gap between mechanistic discoveries and patient-centered care remains the central challenge—and opportunity—for the next generation of clinical and translational research in AA.

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