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Alopecia areata

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ABSTRACT
Alopecia areata (AA) is an autoimmune T-cell mediated type of nonscarring hair loss that presents as round patches affecting up 2% of general population. It affects the nails, hair follicles, and rarely, the retinal pigment epithelium. There is a prevalent family history for most AA patient with human leukocyte antigens (HLAs) class II of chromosome 6q21(HLA-DRB1 for AT and AU, and HLA-DQB1 for patchy AA being a major determinant. It is highly associated with, atopic dermatitis, psoriasis, autoimmune thyroid disease, and allergic rhinitis, rheumatoid arthritis, type 1 diabetes and celiac disease. It can be induced by heavy metal toxicity and viral illnesses (COVID-19, HIV, dengue virus). It is common among males and females aged 20-24 in high SDI countries and incidences are increasing in low-SDI countries. AA is caused by collapse of hair follicle immune privilege leading to autoantigens. It had prominent Th1/IFN- γ response which stimulates the CD8+NKG2D+ effector T cells leading to upregulation of major histocompatibility complexes (MHC I and II) via the JAK-STAT pathway and generate granzyme B (GZMB) to induce apoptotic cell deathOn examination, besides hair loss, the patient had features of exclamation mark hairs and fractured dystrophic hairs. Two assessment tools can be employed to judge the initial starting point of the patient and gauge continued clinical outcomes, these include the Severity of Alopecia Tool (SALT) and the Alopecia Areata Investigator Global Assessment (AA-IGA™). Management can be conversative with use of nonmedical devices or medical with use of topical cortisone, intralesional cortisone injections, oral corticosteroid, Diphenylcyclopropenone (DPCP) or squaric acid dibutyl ester (SADBE); Minoxidil used in adjuvant therapy and JAK inhibitors. Psychosocial aspect of AA must also be addressed as there is usually significant anxiety and depression associated with the condition. Quality of life assessments must be performed early during management as any ongoing stressors can negatively impact disease progression and compliance.

Keywords: Alopecia areata, Alopecia universalis, autoimmune disease and patchy alopecia,

1. INTRODUCTION

Alopecia areata (AA) is a type of nonscarring hair loss that presents as round patches affecting up 2% of general population. [8] It affects the hair follicles, nails and rarely, the retinal pigment epithelium. [1] AA is a common autoimmune alopecia with heterogeneous severity and distribution that is cell mediated by T-lymphocytes against the hair follicular unit. [2] [3]
There are subtypes such as alopecia totalis (AT) (complete hair loss on scalp), alopecia universalis (AU) (complete body hair loss) and alopecia areata focalis aka patchy alopecia, which afflicts more discrete patches of hair of the scalp, eyebrows and eyelashes. [3]
Alopecia Areata is the most common non-scarring alopecia, after male and female pattern alopecia. [4]

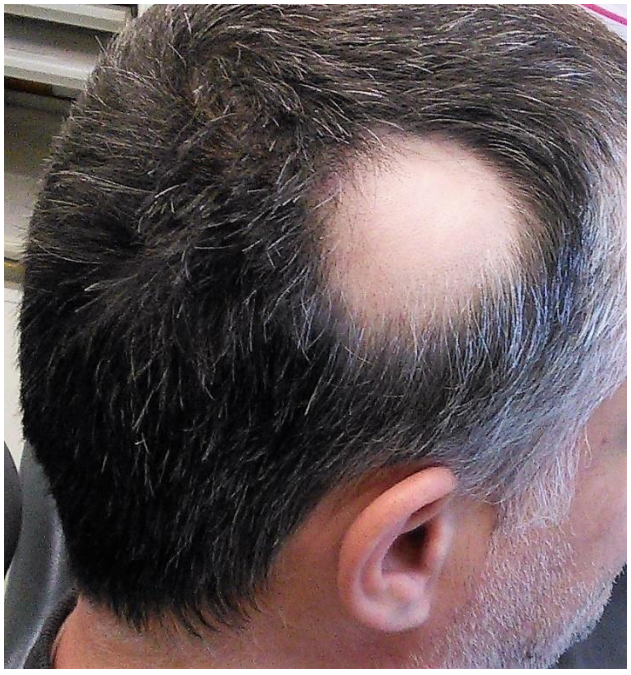

Figure 1: "Alopecia areata" by Thirunavukkarasye-Raveendran is licensed under CC BY 4.0.

2. ETIOLOGY

There are environmental and genetic factors that influence the development of alopecia areata, however, alopecia areata has a significant genetic basis evident by a 55% concordance rate between identical twins. [1] There is a prevalent family history in adults up to 8.6% and among children, up to 51.6% with skewing among adult males in one study. [4] It was established that human leukocyte antigens (HLAs) class II of chromosome 6q21(HLA-DRB1 for AT and AU, and HLA-DQB1 for patchy AA are a major determinant for AA and could be useful to determine severity phenotypes.[5] Environmental causes are toxic metals such as thallium (Tl), arsenic (As), and mercury (Hg) with consideration for acute/chronic exposure

of cadmium (Cd), bismuth (Bi), copper (Cu), and lithium (Li) can cause AA in humans. [6] There is an association low serum zinc levels and AA suggesting zinc deficiencies should also be considered as a pathophysiologic mechanism for AA presentation, especially in children and newborn infants. [6] A nationwide study between 1996-2008 in using 4334 patients with AA in the National Health Insurance Database in Taiwan concluded a significant associated with vitiligo, lupus erythematosus, psoriasis, atopic dermatitis, autoimmune thyroid disease, and allergic rhinitis. Thyroid disease (hypo/hyper undifferentiated in study) was highly related to AA. As well as rheumatoid arthritis, type 1 diabetes and celiac disease. [7] [31] The COVID-19 pandemic resulted in new numbers of AA relapses or onset after infection or vaccination. Other viruses such as human immunodeficiency virus (HIV), cytomegalovirus (CMV), dengue virus, as well as the Hepatitis B vaccine are also associated with AA. [30] Rapid weight loss and use of weight loss drugs (amphetamines eg clobenzorex) are also risk factor for AA. [19]

3. EPIDEMIOLOGY

Data from the Global Burden of Disease (GBD) between 1990 to 2019, the male-to-female ratio of AA peaked in 20-24 years old globally high-SDI, high-middle-SDI, middle-SDI, and low-middle-SDI regions but in low-DSI region ages peaked at 90-94 age group. However, it was highest among females ages 30-34 years across all SDI regions. Countries with the largest increase in incidence were Kuwait, South Sudan and Nigeria. Regionally, the age-standardized incidence rate and DALY rate increased significantly in Western Sub-Saharan Africa and South Asia rationalized by poor living environment and propensity of inflammation, infection or autoimmune disease. Associated lack of nutrients such as zinc and folic acid. [9]

The incidence of AA in low-income countries could be underestimate due to the low self-reported cases, poor health wellness, and patients with mild alopecia not considering medical intervention. The overall global burden is likely underestimated. It should be noted that the incidence of AA is higher in children than adults. [2]

4. HISTOPATHOLOGY

Varies during the disease stages.
Acute and subacute stages:
“Peribulbar lymphocytic infiltrate in a “swarm of bees” pattern composed of CD4+ and CD8+ T-cells around anagen follicles. With features of follicle miniaturization.
Edema, microvesiculation, apoptosis, macrophages and foreign body giant cells around the hair follicles”.
Chronic stage:
Catagen and telogen hairs increase +/- active inflammation. Pigmentary incontinences.
Recovery stage:
Minimal inflammation and anagen hair increases. [10] [11] [12]

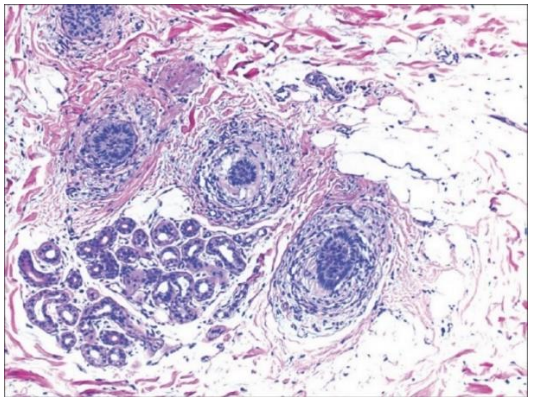

Figure 2; Showing "Swarm of bees" pattern of lymphocytes surrounding the hair follicle.

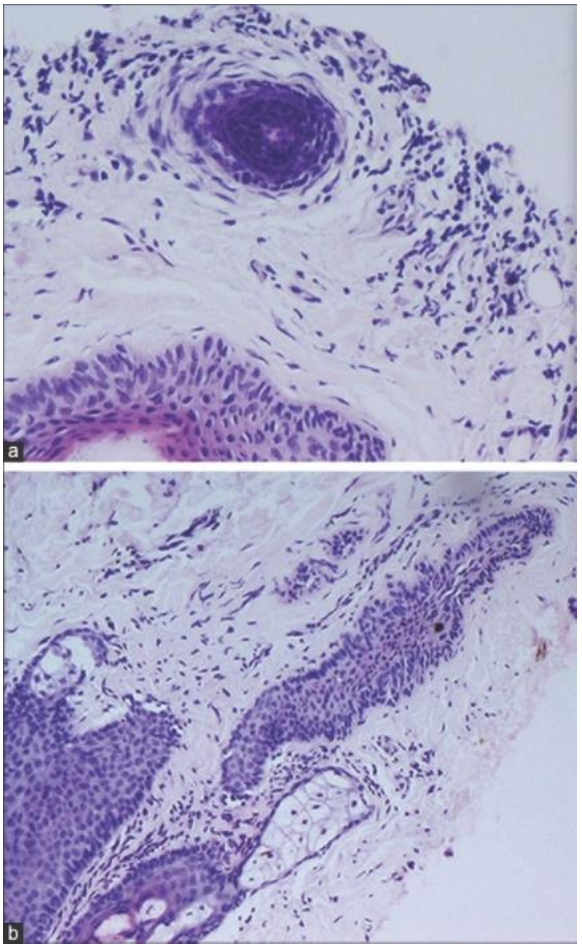

Figure 3: Showing Histopathology (H and E, ×100) (a) peribulbar lymphoid infiltrate (b) follicular stellae and telogen unit hairs.

5. IMMUNOPATHOGENESIS

The anagen hair bulb, responsible for hair growth, is influenced by various immunosuppressive factors such as α-MSH, TGF-beta, and IGF-1. Additionally, NK-cell suppression plays a role. During an inflammatory event, MHC class Ia expression increases

within the hair follicle, leading to autoimmunity through autoantigen presentation by MHC class I molecules in the anagen hair bulb. [13,14,28,36]

In AA lesions, Th1 chemokines (CXCL9, CXCL10, and CXCL11) and Th2 cytokines (IL-13, CCL18, CCL26, TSLP) are significantly expressed. These molecules are also upregulated in the serum of AA patients. [13-15]

In mouse studies involving grafted AA, researchers observed increased expression of the CXCR3 ligand within the hair follicle. Hair follicles infiltrated by CD8+ T cells expressed the CXCR3 receptor. Proinflammatory cytokines and chemokines recruit CXCR3+ T cells, suggesting their involvement in AA pathogenesis. [15]

Anti-CXCR3 ligand treatment delayed and prevented AA development in mice. However, whether this blockade can reverse established disease remains an area for further investigation. [15]

6. Signs and Symptoms

Table 1; Showing the Signs and Symptoms Associated with Alopecia Areata

SIGNS	SYMPTOMS
Hair loss, well circumscribed patches (scalp or beard), total scalp hair loss, or whole body hair loss [1] [4] bilateral, patchy eyebrow loss [16] bilateral, patchy eyelash loss in the upper and lower eyelids [16] Exclamation point hairs (narrow and fall out easily) [1] [4] Koilonychia [17] Trachyonychia [1]	Nonspecific but there may be associated comorbidities to screen for; see complications.

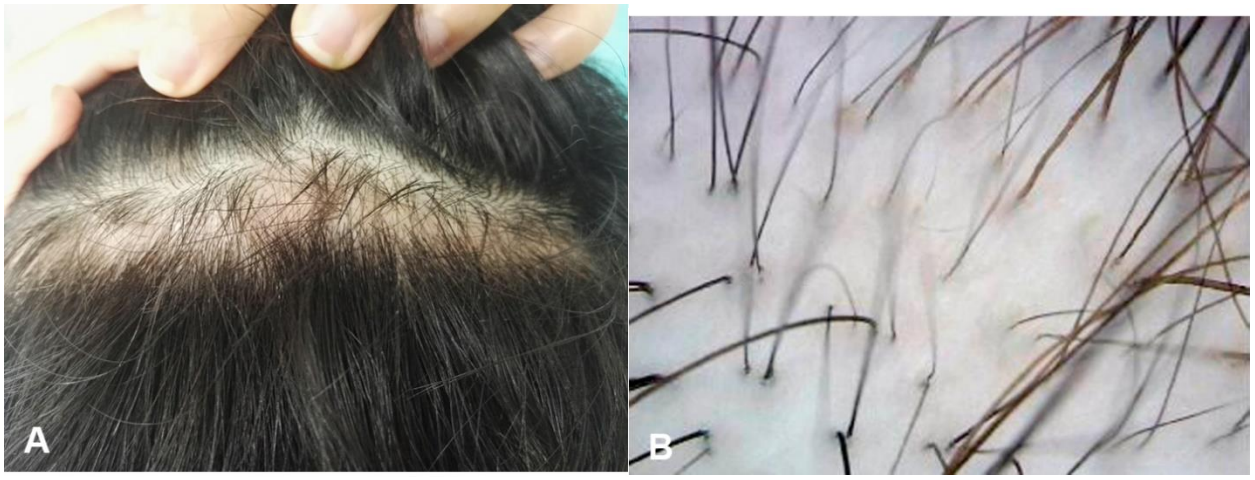

Figure 4 A, The clinical manifestation. Image 4 B, The trichoscopic evaluation.[12]

This is a case of a 28-year-old man with a 4-year history of linear hair loss. 10cm long by 2 of the parietal scalps. Skin was smooth, normal color or atrophy or scales. Hair pull test was perilesional trichogram were normal. Trichoscopic evaluation showed short vellus hair. [12]

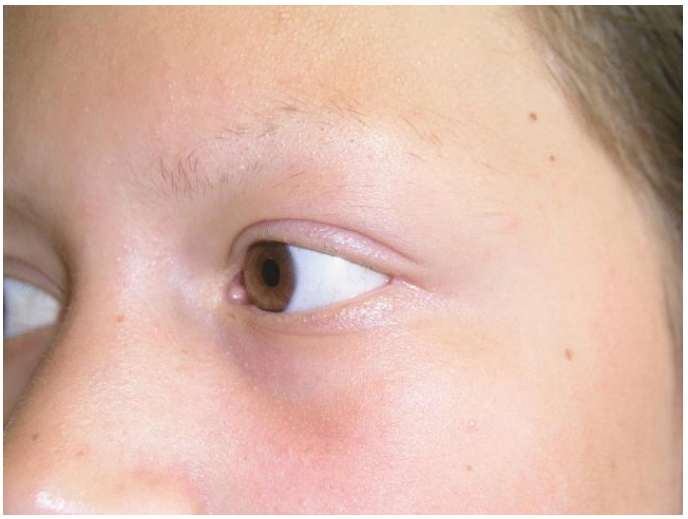

Figure 5; Showing patient with alopecia areata presenting with patchy eyebrow loss and patchy eyelash loss of the upper and lower eyelids [16]

Investigations

"Alopecia areata is usually diagnosed based on clinical manifestations, but dermoscopy/trichoscopy and histopathology can be used to assist diagnosis. [4]
Trichoscopic evaluation of the scalp is based on follicular patterns, interfollicular patterns and hair signs". [18] For AA, it is dependent on stage and severity of disease. Black dots, tapering hairs and cadaverized hairs are usually observed. In longstanding AA, dystrophic hairs, fractured roots, Pohl–Pinkus's constriction and telogen hairs with empty follicles can be observed. Some short vellus hairs in regrowth phase may be observed. [18] [19]

Figure 6: Showing Trichosopy-presence of exclamation mark hairs (black arrow) and black dots (cadaverized hairs-white arrow) suggest active alopecia areata (Dermlite foto ii pro - polarized light mode) [35]

There are no other associated complications of the disease besides the progression of the disease, the underlying risk factors and treatment of choice. [1] There is a significant psychological load on the patient due to the cosmetic aspect of the disease. [20] In a Nepali survey of 75 AA patients conducted in a dermatology outpatient clinic revealed that 66.7% and 73.3% had depression and anxiety respectively. The majority (82%) had minimal depression with non-having severe depression and 89.0% had mild anxiety with non-having sever anxiety. [20] One German study saw the rates of anxiety being the same among males and females above the 30-age group. Depression in the 30-49 age group was also high but skewing to females. Female patients ages 30-49 are most vulnerable to develop a co-occurring mental disorder. [34] "In one study the Dermatological Life Quality Index (DLQI) score of the participants with alopecia was comparable to that of severe psoriasis and atopic dermatitis. [21] It was recommended that that Quality of Life (QoL) impairment and mood disorders should be considered and managed in all individuals with AA". [20]

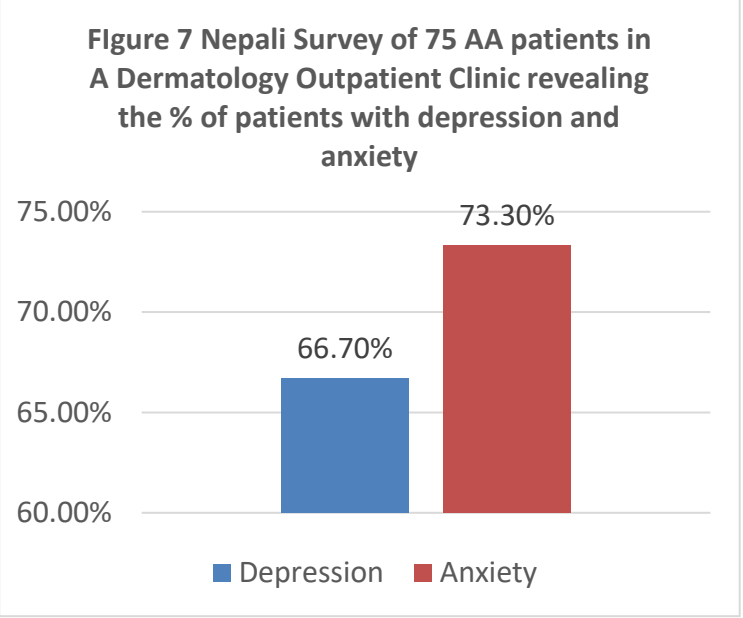

FIgure 7 Nepali Survey of 75 AA patients in A Dermatology Outpatient Clinic revealing the % of patients with depression and anxiety

Differential Diagnoses

Table 2: Showing the Differential of Alopecia Areata Classified by Non-scarring and Scarring Alopecia	
Other non-scarring alopecia;	Scarring alopecia
Androgenic alopecia aka male pattern hair loss Female pattern hair loss Telogen effluvium; triggered by stressful events eg major illness or surgery Tinea capitis; fungal infection of scalp Temporal alopecia triangularis; newborns and children; triangular bald sport with vellus hairs. Lipedematous alopecia; thickening of the subcutaneous layer which is soft, boggy and doughy associated with hair loss	Lichen planopilaris: causes permanent fair follicle destruction Frontal fibrosing alopecia; affects postmenopausal women, type of lichen planopilaris Chronic cutaneous lupus erythematosus; characterized by ill-defined, round plaques with atrophy and hypopigmented spots. Folliculitis decalvans; inflammation of the hair follicle due to staph aureus colonization.
[4] [[22] [23] [24] [25] [26]	

Other conditions that can present similarly as AA:

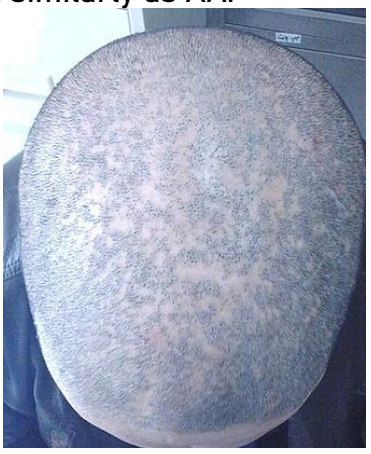

Figure 8: Tinea capitis.jpg" by Gholamreza Baqeri is licensed under CC BY 4.0 International

Figure 9: "Male Pattern Baldness" by emilio labrador is licensed under CC BY 2.0.

Management

"In order to assess starting point and end goals of management of the condition the Severity of Alopecia Tool (SALT) is widely used to assess the extent of scalp hair loss. Treatment success is defined as 50% improvement in scalp hair; however, patient perspectives are unknown". [27][29] One study developed the Alopecia Areata Investigator Global Assessment (AA-IGA™) which includes 5 categories. Majority of clinicians and patients of this study agreed that for patients with more than 50% scalp- hair loss, successful treatment would be hair regrowth resulting in <20% scalp-hair loss. [27]

Alopecia Areata Investigator Global Assessment™ (AA-IGA™)

	None 0	Limited 1	Moderate 2	Severe 3	Very Severe 4
Please rate the patient's **scalp hair loss**, as it looks **today**.	0%	1-20%	21-49%	50-94%	95-100%

The Severity of Alopecia Tool (SALT; Olsen et al 2004) is recommended to assess the extent (0-100%) of scalp hair loss.

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Figure 10; Showing the Alopecia Areata Investigator Global Assessment (AA-IGA™) [27]

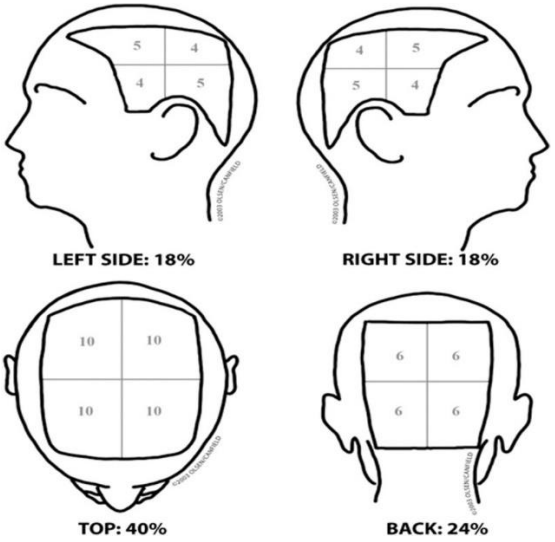
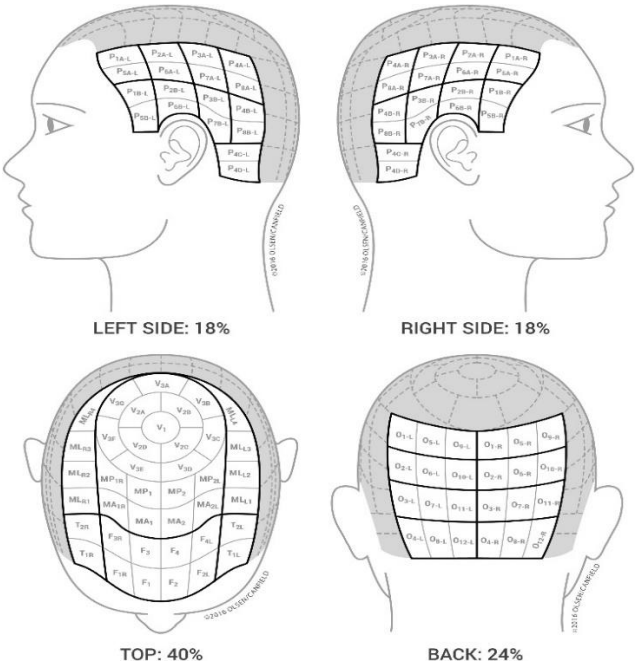


Figure 11: Showing SALT I aid for determining scalp surface area.[29]

"Used by visually moving the remaining terminal hair together to what looks like normal density and then determining the % of the bald scalp remaining. This is multiplied by the percentage of the chart for each quadrant and added for a total surface area percentage".

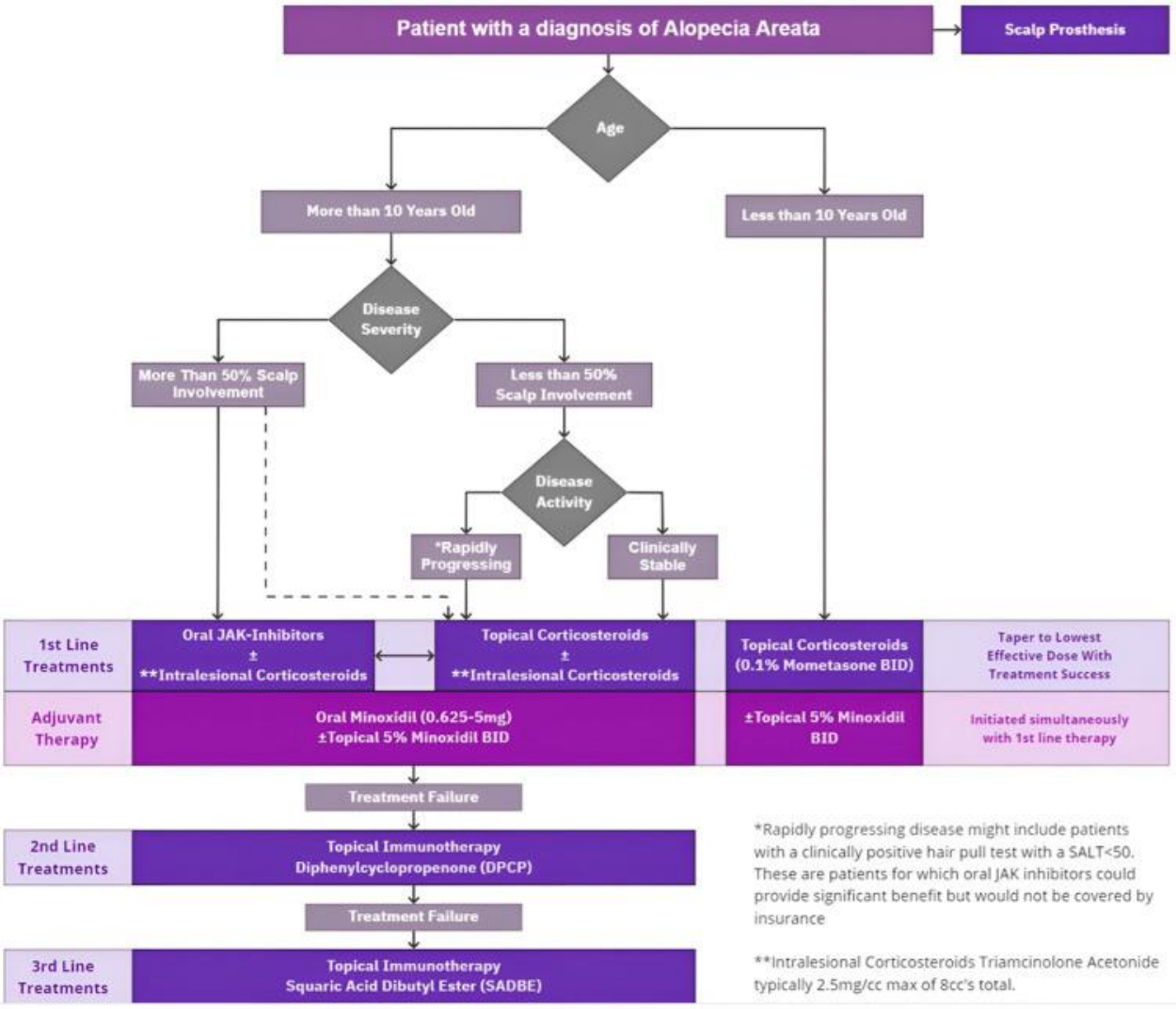


This is the SALT score.
Figure 12: 2SALT II aid for determining scalp surface area more precisely. [29]

The SALT score, using either the original SALT I or SALT II, is determined by adding the percentage hair loss in the various areas of the scalp. With the addition of hair density, SALT II can also be used to establish patterns of hair loss germane to different hair loss conditions.

Treatment options include; nonmedical intervention such as microblading, hair prosthetics, and patient choice of no treatment at all due to high probability of self-resolution. [30]
Modest to high success treatment options include; topical steroids, topical immunotherapies, intralesional steroids, systemic corticosteroids and JAK inhibitors (baricitinib, for the treatment of AA in patients with SALT scores greater than 50).
Treatment with variable success include; topical calcineurin inhibitors, cryotherapy (light spray jet), topical latanoprost or bimatoprost, pulsed infrared diode laser (904 nm), methyl-aminolevulinic acid photodynamic therapy, ntihistamines and 308-nm excimer laser. Evidence of success is limited. [30]
Make note of other areas of hair loss besides the scalp. In one study when asked the importance of the scalp versus the eyebrows 40.6% responded that scalp hair was more important, 33.6% responded that both were equally important, and 26.8% responded that eyebrows were more important. 48.2% of subjects reported that they would like both eyebrows and scalp hair to be treated out of a1,741 adults. [32]

One recommends the outlined the decision tree below.



Flowchart 1; Showing the recommend treatment outline for alopecia areata [30]

Table 3 showing the Alopecia Areata Treatment Options, Dosing and Outcomes; modified from [30] "Alhanshali L, Buontempo MG, Lo Sicco KI, Shapiro J. Alopecia Areata: Burden of Disease, Approach to Treatment, and Current Unmet Needs. Clin Cosmet Investig Dermatol. 2023 Mar 31; 16:803-820. doi: 10.2147/CCID.S376096. PMID: 37025396; PMCID: PMC10072216".
[31]

Therapy option		Dosing	Outcomes
Topical cortisone		"Topical 0.1% betamethasone valerate foam applied twice daily for 12 weeks topical mometasone 0.1% solution or cream twice daily for children clobetasol propionate 0.05% as either a foam, cream, ointment, or solution for adults"	"75% hair regrowth in mild to moderate AA"
Intralesional cortisone injections		"Intralesional 10 mg/mL triamcinolone acetonide after 12 weeks of treatment"	"> 50% improvement in patients with patchy AA and eyebrow loss"
Oral corticosteroid		Oral prednisone	For active hair fall, assists turning off disease activity.
Diphenylcyclopropenone (DPCP) or squaric acid dibutyl ester (SADBE);		"This intentionally induces allergic contact dermatitis to shift T cell mediated autoimmunity away from hair follicle. To remain on the scalp for 48 hr while it is covered with a wig or protective cap to prevent light exposure"	Success rates of approximately 60 to 70%
"Minoxidil used in adjuvant therapy, poor success as monotherapy. Oral or topical. Topical yields good cosmetic"	Oral minoxidil monotherapy	5 mg twice a day	18% of patients with less than 75% hair loss achieved a cosmetic response
	Oral Minoxidil with Tofacitinib	"Tofacitinib 5 mg twice daily and oral minoxidil 2.5 mg two or four times a day"	At least 50% regrowth in 41.7% of patients

results for patchy alopecia.			
JAK inhibitor		"JAK inhibitors. Best used in resistant or Alopecia totalis/universalis. Baricitinib 2 mg or 4 mg approved by FDA Other options ; tofacitinib, ruxolitinib, Dosing variable"	Efficacy range varies

Psychosocial management of the patient:
As mentioned earlier, psychological impact of AA can be devastating for the patient. Encourage scalp care and skin health despite hair loss. Encourage used of soap made for scalp skin, use of cosmetic camouflages. Assess impact on patient's home and work life and relationships. [31] This is a high association of AA with psychosocial comorbidity in both adult and pediatric patients. Families should be counseled on the effects. Stressful life events can precede new onset AA and continues stress can compromise management. Encourage use of individual therapy, peer support groups, family support groups and education and awareness in school and on a mainstream level. [33]

Conclusion

Alopecia areata is easily diagnosed clinically, however, it is a complex multifactorial disease with extreme disease burden on society and psychosocial consequences on the individual with this condition. When managing AA, it is important that a thorough clinical history is performed to be informed about any underlying causes or comorbidities that can influence management and expected outcomes. AA can be very distressing to patients and it is the role of the clinician to acknowledge patient concerns, offer adequate medial therapy and resources to ensure best clinical outcomes.

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