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Objective Outcome Measures: Collecting Meaningful Data on Alopecia Areata

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Capsule summary:

- Currently the only standardized method of assessment of alopecia areata is the SALT score
- This article offers recommendations for standardized assessment and response criteria in patients with alopecia areata.
- These methods will facilitate direct comparison of alopecia areata treatment outcomes in both clinical practice and clinical trials

Objective Outcome Measures: Collecting Meaningful Data on Alopecia Areata

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Key words:

- Alopecia areata
- Outcome measures
- Response criteria
- SALT score
- ALODEX score
- Assessment measures

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- Currently the only standardized method of assessment of alopecia areata is the SALT score
- This article offers recommendations for standardized assessment and response criteria in patients with alopecia areata.
- These methods will facilitate direct comparison of alopecia areata treatment outcomes in both clinical practice and clinical trials

Abbreviations:

AA: Alopecia areata

AT: Alopecia totalis

AU: Alopecia universalis

ALODEX: Alopecia Density and Extent

BL: baseline

LAD: Lesional alopecia and density

mSALT II: modified SALT II diagram

SALT: Severity Alopecia Tool

SALT I: SALT I diagram

Abstract:

- **Background:** Although alopecia areata is a common disorder, it has no FDA approved treatment and evidence-based therapeutic data is lacking.
- **Objective**: To develop guidelines for the diagnosis, evaluation, assessment, response criteria and endpoints for alopecia areata.
- **Methods**: Literature review and expert opinion of a group of dermatologists specializing in hair disorders.
- **Results:** Standardized methods of assessing and tracking hair loss and growth including new scoring techniques, response criteria and endpoints in alopecia areata are presented.
- **Limitations:** The additional time to perform the assessments is the primary limitation to use of the methodology in clinical practice.
- **Conclusion:** Use of these measures will facilitate collection of standardized outcome data on therapeutic agents used in alopecia areata both in clinical practice and in clinical trials.

I. Background:

Alopecia areata (AA) is a common condition, affecting 1.7-2.1% of the general US population at some point during their lives.[1,2] Multiple treatments are available but none are currently approved by the Food and Drug Administration (FDA) for this indication and there is no consensus agreement on their use in clinical practice. The lack of standardized assessment methods and the necessity of taking into account the effect of extent, pattern, and duration of hair loss on regrowth have been barriers to clinical trials in AA. However, with the advent of electronic medical records and large collaborative databases, we now have an opportunity to collect data on large numbers of patients with AA seen in clinical settings. In addition, there is renewed interest in the FDA approval of new medications for AA.

A necessary component of collecting comparative data on therapeutic outcomes from both clinical databases and clinical trials of AA is the creation and acceptance of standardized diagnostic criteria, assessment measures, response criteria and endpoints. The following are recommendations by a group of dermatologists with expertise in hair disorders who first convened at Duke University on July 10, 2015 to address this issue.

II. Diagnosis of AA:

A. Characteristic features

1. Follicular ostia are intact and visible by either direct visualization or by dermatoscopic evaluation
2. Complete loss of all terminal hair in at least one area of hair loss
3. Increased hair shedding. Documentation by a gentle pull on a group of hairs at the periphery of patches of hair loss repeated in several areas of the scalp. The proximal ends of pulled hairs should be examined microscopically: telogen hairs alone, a combination of telogen and

dystrophic anagen hairs, or broken hairs are typical findings.[3-5] Finding multiple hairs on at least 5 pulls of the scalp hair is indicative of "*active progressive hair loss.*"

4. Lack of perifollicular erythema or scale, pustules or other signs of active follicular inflammation.

B. Supportive features:

1. Exclamation point hairs. Aldersmith in 1897[3] provided an excellent description of these hairs: "*A few small broken hairs are generally to be seen at the edges of the patches; ... club-shaped stumps about an eighth of an inch long….like a note of admiration (!) without the dot. These stumps are very easily extracted entire on traction instead of breaking off".* On microscopic exam, the distal ends of these exclamation point hairs show a trichorhexis nodosa-like change. Exclamation point hairs may also be seen in anagen effluvium[6] and are another sign of *active progressive hair loss*.

2. Body hair loss in patches or loss of eyelashes or eyebrows

3. Fine pitting of nails, trachyonychia (denoting the entire nail plate is rough or thin with or without longitudinal ridging, often likened to "sandpapered" nails) or 20 nail dystrophy

4. Dermatoscopic findings of yellow and/or black dots [7]

II. Recommendations for initial (and follow-up) evaluation (Supplemental Tables IA and IB):

A. History: We have narrowed the data from the initial Alopecia Areata Investigational Guidelines[8] to those factors that may affect either choice or response to treatment (Table I).[9-23]

B. Physical exam:

1. Severity of hair loss:

The classification of severity of AA , first published by Olsen in 1992[24] and 1997[25], formalized by the NAAF Guidelines Committee in 1999[8] and revised in 2004,[26] categorizes the scalp (S) terminal hair loss as follows: none (S_0), 1-24% (S_1), 25-49% (S_2), 50-74% (S_3), 75-99% (S_4) [including 75-95% (S_{4a}) and 96-99% (S_{4b})] and 100% scalp hair loss (S_5) (Table II). Severity also

includes the extent of body hair loss and is classified as none (B_0), some (B_1) or total loss (B_2). Alopecia totalis (AT) can thus be S_5B_0 or S_5B_1 but alopecia universalis (AU) can only be S_5B_2

2. Pattern of hair loss: There are four main patterns of scalp hair loss in AA: patchy, diffuse (decrease in density diffusely over scalp), ophiasis (decrease in bandlike presentation in parietal and occipital areas), and totalis. The patchy subtype may remit quickly, be persistent with waxing and waning over time, or progress to total hair loss. The ophiasis pattern of hair loss and alopecia totalis (AT)/universalis (AU) have a lower spontaneous remission rate and lower rate of response to therapy. [9,10,12-17] The diffuse subtype is rare.
3. Activity of hair loss. There are two quick methods of determining the overall activity of hair loss in AA.
    a. The presence of "exclamation point hairs" at the periphery of bald areas. These should be differentiated from new regrowing hairs which have a tapered distal tip.
    b. Positive AA hair pull. Unlike the "hair pull" done in cases of telogen effluvium where the number of hairs removed on a given hair pull may have implications for diagnosis and response to treatment, a "hair pull" in AA is primarily qualitative.
4. Nail involvement.

    Although the original classification of AA indicated that N_2 should only apply when all 20 nails are affected by trachyonychia ,[8] the current authors have modified this classification (Table II).

C. Scalp biopsy: Biopsy may not always show the classic perifollicular or peribulbar lymphocytic infiltrate but may instead show a very high percentage of miniaturized hairs and catagen/telogen hairs.[27] A biopsy may be necessary to confirm a diagnosis of diffuse AA.

III. Assessment of AA

A. One or more of the following methods should be chosen for use at the start of any given therapy and during follow-up visits. Table III details how each technique might best be utilized.

1. Global assessment for those patients treated with systemic agents or whole scalp skin-directed therapy.

   a. Percentage scalp hair loss:

      i. Severity Alopecia Tool (SALT) Score:

         The SALT I visual aid [8] first published in 1999 and updated in 2004,[26] significantly helps one to visualize the amount of terminal hair loss in each of 4 quadrants of the scalp and then upon summing these, generates the total percentage of scalp hair loss or SALT score (Figure 1). The SALT score captures the total area of the scalp bereft of any terminal hair.

      ii. Alopecia Density and Extent (ALODEX) score[28]

         The SALT II visual aid first published in 2016,[29] with subsequent minor modification (Figure 2), is core to calculating the ALODEX score and to tracking specifics of the hair loss over time. The ALODEX score combines both extent and hair density into an overall % scalp hair loss. Although it is possible to calculate by paper scoring, an iPAD app makes it possible to score all the 1% areas quickly and to generate electronically the total ALODEX score. . An example of both SALT and ALODEX grading of scalp hair loss for a representative patient with AA is given in Figure 3.

   b. Extent of scalp hair loss [% scalp surface area (SSA) that has any degree of hair loss]

      The ALODEX methodology (mSALT II plus iPAD app documentation of the density of each 1% area of the scalp) can also independently determine the extent of hair loss, not just the percent of scalp with baldness. This may have added utility for quantifying the amount per cm^2 of topical medication applied and could potentially be an independent

prognostic factor. The ALODEX methodology also allows (1) tracking of density in target bald patches or regions of hair loss as the hair loss progresses or improves over time and (2) confirmation of patterns of hair loss (example ophiasis).

c. Alopecia Areata Progressive Index[30]

Introduced in 2016, this method includes determining the percent scalp hair loss per quadrant using the SALT I visual aid, multiplying this number by a hair loss activity score and then summing the products of each quadrant. This activity score is based on (1) hair pull and (2) dermatoscopic findings of exclamation point hairs, broken hairs and black dots in a representative area of each quadrant.

2. Half head assessment:

This method is often used to assess the response of chemical sensitizers or topical agents in patients who have extensive AA by determining the amount of hair loss on the treated versus untreated sides of the scalp pre-treatment and at follow-up visits.[31] One could use a modification of the SALT or ALODEX score to assess hair loss on each side of the scalp. If hair growth occurs only on the treated side, it is presumed to be entirely related to the agent applied. However, if there is hair growth on both sides of the scalp, explanations include spontaneous remission, systemic absorption by the topical agents, diffusion of the agent to the untreated side of the scalp, and inadvertent or purposeful application by the patient of agent to both sides of the scalp

3. Lesional assessment. This has utility primarily for patches of hair loss that are treated with topical or intralesional agents.

a. Lesional size: Designation of 1-3 target areas of hair loss, preferably the largest ones and ones that show active progressive hair loss by hair pull or presence of exclamation point hairs and determination of area covered by each and collectively (Figure 4).

b. The Lesional Area and Density (LAD) score: This combines a density score (using a 100 point density scale compared to normal) with the area of each target lesion (Figure 4). If multiple target areas are utilized, the sum of all individual LAD scores is the overall LAD score.

4. Adjuvant measurements

a. Hair pigmentation. The percentage of natural color (non-dyed) or white hair should be noted at the beginning and end of treatment.

b. Vellus hair. Given that the SBN classification, SALT score, and the ALODEX score only grade terminal hair, vellus hair would not typically be noted. However, the percentage scalp coverage of vellus hair could be determined by SALT or ALODEX score as a potential prognostic indicator..

c. Activity of hair loss. As noted above, evaluation for both exclamation point hairs and a gentle hair pull at the periphery of several patches of hair loss will help to determine active progressive hair loss. In active patches, dermoscopy shows black dots, broken hairs of various lengths and exclamation mark hairs.

B. Patient assessment:

What patients find meaningful in terms of response will be related to the severity of hair loss at baseline, and if the remaining alopecia is able to be camouflaged. Some options for quantifiable assessment methods by patients include:

1. Classification of hair loss. We recommend that patients perform self- assessment of their hair loss using the scalp (S) terminal hair loss categorization ie S_0-S_5. Performing this exercise with the patient will enable investigators/clinicians to determine how extensive patients feel their hair loss is and facilitate further discussion and education about their AA. A more explicit query would be what % overall hair loss the patient feels he or she has which will be able to be correlated with the SALT or ALODEX scores.

2. Quality of life: There are several quality of life instruments available for skin disorders or hair loss that could be modified for use in AA.[35-39]

C. Role of photographs: Given the dynamic nature of hair loss in AA and the typical time interval between clinic visits, it is important to have photographic documentation of the hair loss at least at the start of treatment. Photographic views of the top, sides, and back of the scalp and face with hair pulled back to expose frontal hair line, eyebrows and eyelashes are best for documentation. However, if patients have multiple patches of hair loss, one may need to part the hair in multiple areas to unmask the different areas of hair loss and take additional photographs of each area of hair loss in a serial manner. Standard photographs to document extent of hair loss cannot be done in patients with attached hair pieces.

We also recommend that for patients being followed in clinic, that physicians consider also taking photographs of the hair loss with the patient's cell phone (if this option is available). The latter allows the patient to have a record of his/her own hair loss and allows sharing of subsequent photographs by the patient with the physician without concerns of HIPAA violation.

IV. Recommended response scores:

A. Global: Percent change from baseline in SALT or ALODEX score.

B. Lesional (see Figure 4):

1. Percent change from baseline of target area size.
2. Percent change from baseline in LAD score.

C. Patient generated: Using a simple scale for change in hair growth such as +1 to +3 (slightly, moderately, greatly increased), 0= no change, and -1 to -3 (slightly, moderately or greatly decreased[34] may help to correlate patient appreciation of changes in hair growth with the physician generated SALT or ALODEX scores.

V. Endpoints:

A. Primary endpoint: Physician assessment of change in hair growth from baseline.

Although the goal of treatment is to return the patient's scalp hair to that present before the current AA episode, the hair density and any male or female pattern hair loss present pre-AA episode cannot be documented. Because of this, determination of 100% regrowth by SALT or ALODEX scoring is not feasible and instead, a 50% improvement in SALT or ALODEX score, ideally with diffuse scalp coverage, is a reasonable target for efficacy of a treatment for AA. In addition, spontaneous remission in AA has to be considered in assessing efficacy : this can be relatively high in patchy AA[32] and has been documented to be as high as 8% over a 3 month period of time in extensive AA (>50% scalp hair loss).[33]

Time for regrowth should be taken into account in determining efficacy. Often topical medications, such as corticosteroids or anthralin, take 3-4 months for obvious hair growth and when it occurs, it will likely not be uniform in all areas treated but steadily regrow with continued use. Patients treated with intralesional steroids can usually expect some hair growth in about 4-6 weeks if effective, although the hair growth may be patchy in the areas of injections secondary to uneven distribution of the injected medication or the variable responsiveness of individual follicles to this treatment modality. Systemic medications such as corticosteroids or other immunomodulators usually show more diffuse hair growth beginning at 4-6 weeks. To determine the efficacy of any new agent for AA, it is recommended that at least a 12 week evaluation period be performed.

C. Secondary endpoints. Patient assessment of moderately increased hair growth may be the equivalent of a physician 50% change from BL but further data on this issue is needed. A certain level of change in QoL instrument could also be considered a secondary endpoint if validated.

VI. Conclusions:

We realize that most practitioners will not be able to collect all the information we recommend at each visit on all patients with AA. However, we do recommend obtaining some very basic information that could assist in determining which treatments work best for certain subtypes of AA and in association with which prognostic factors. The collection of standardized outcomes data by large numbers of dermatologists, along with data generated by clinical trials, should help establish best treatment practices for this challenging condition.

References:

1. Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton J. Incidence of alopecia areata in Olmsted County, Minnesota, 1975-1989. Mayo Clin Proc 1995;70:628-633.
2. Mirzoyev SA, Schrum AG, Davis MD, Torgerson RR. Lifetime incidence risk of alopecia areata estimated at 2.1% by Rochester Epidemiology Project, 1990-2009. J Invest Dermatol. 2014;134(4);1141-1142.
3. Aldersmith H. Ringworm and Alopecia Areata. Their Pathology, Diagnosis and Treatment. H K Lewis, London, 1897.
4. Van Scott EJ. Evaluation of disturbed hair growth in alopecia areata and other alopecias. Ann Ny Acad Sci 1959;83:480-490.
5. Olsen EA. Clinical tools for assessing hair loss. In Olsen EA (Ed): *Disorders of Hair Loss: Diagnosis and Treatment.* McGraw-Hill, NY, NY, 2003
6. Pirmez R, Pineiro-Maceira J, Sodre CT. Exclamation marks and other trichoscopic signs of chemotherapy induced alopecia. Australas J Dermatol 2013;54:129-32.
7. Miteva M, Tosti A. Hair and scalp dermoscopy. J Am Acad Dermatol 2012;67:1040-1048.
8. Olsen EA, Hordinsky M, McDonald-Hull S et al. Alopecia areata investigative guidelines. J Am Acad Dermatol 1999;40:242-246.
9. Walker SA and Rothman S. Alopecia areata. A statistical study and consideration of endocrine influences. J Invest Dermatol 1950;14:403-413.
10. Tosti A, Bellavista S, Iorizzo M. Alopecia areata: a long term follow-up study of 191 patients. J Am Acad Dermatol 2006;55:438-441.
11. De Waard-van der Spek FB, Oranje AP, De Raeymaecker DM, Peereboom-Wynia JD. Juvenile versus maturity-onset alopecia areata--a comparative retrospective clinical study. Clin Exp Dermatol. 1989;14(6):429-33.

12. Colombe BW, Price VH, Khory EL, Garovoy MR, Lou CD. HLA Class II antigen associations help to define two types of alopecia areata. J Am Acad Dermatol 1995;33:757-764.
13. Wiseman M, Shapiro J, MacDonald N, Lui H. Predictive model for immunotherapy of alopecia areata with diphencyprone. Arch Dermatol 2001;137: 1063-1068.
14. Uchiyama M1, Egusa C, Hobo A, Irisawa R, Yamazaki M, Tsuboi R. Multivariate analysis of prognostic factors in patients with rapidly progressive alopecia areata. J Am Acad Dermatol. 2012;67(6):1163-1173.
15. van der Steen PH1, van Baar HM, Happle R, Boezeman JB, Perret CM. Prognostic factors in the treatment of alopecia areata with diphenylcyclopropenone. J Am Acad Dermatol. 1991;24(2 Pt 1):227-230.
16. MacDonald Hull SP, Wood ML, Hutchinson PE, Sladden M and Messenger AG. Guidelines for the management of alopecia areata. Brit J Dermatol 2003;149:692-699.
17. Olsen EA. Investigative guidelines for alopecia areata. Dermatol Therapy. 2011;24(3):311-319.
18. Ikeda T. A new classification of alopecia areata. Dermatologica 1965;131:421-445.
19. Anderson I. Alopecia areata: A clinical study. Br Med J 1950;Dec 2:1250-1252.
20. Freyschmidt-Paul P, Happle R, McElwee KJ, Hoffmann R. Alopecia areata: treatment of today and tomorrow. J Invest Dermatol Symp Proc 2003;8:12-7.
21. Weise K, Kretzschmar L, Jonh SM, Hamm H. Topical immunotherapy in alopecia areata: anamnestic and clinical criteria of prognostic significance. Dermatology 1996;192:129-133.
22. Petukhova L, Duvic M, Hordinsky M, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature 2010;466(7302):113-117.
23. Nelson DA, Spielvogel RL. Alopecia areata. Int J Dermatol 1985;24:26-34.
24. Olsen EA, Carson SC, Turney EA. Systemic steroids with or without 2% topical minoxidil in the treatment of alopecia areata. Arch Dermatol 1992;128:1467-1473.

25. Olsen EA. Topical and systemic corticosteroids in alopecia areata. Austral J Dermatol 1997;38:20.

26. Olsen EA, Hordinsky MK, Price VH, Roberts JL, Shapiro J, Canfield D et al.: Alopecia areata investigational assessment guidelines – Part II. J Am Acad Dermatol 2004;51:440-447.

27. Whiting DA. Histopathologic features of alopecia areata: a new look. Arch Dermatol 2003;139:1555-1559.

28. Olsen EA, Green C, Hordinsky M et al. Alopecia Density and Extent Score (ALODEX): a new method for assessing severity of hair loss in alopecia areata. Submitted for publication.

29. Olsen EA, Canfield D. SALT II: A new take on the Severity of Alopecia Tool (SALT) for determining percentage scalp hair loss. J Am Acad Dermatol 2016:75(6):1268-1270.

30. Jang YH, Moon SY, Lee WJ et al. Alopecia areata progression index, a scoring system for evaluating overall hair loss activity in alopecia areata patients with pigmented hair: a development and reliability assessment. Dermatology 2016;232:143-149.

31. van der Steen PHM, Happle R. Topical immunotherapy of alopecia areata. Derm Clinics 11:1993: 619-622.

32. Messenger AG, McKillop J, Farrant P, McDonagh AJ, Sladden M. British Association of Dermatologists' guidelines for the management of alopecia areata 2012. Brit Assoc Dermatol 2012;166:916-926.

33. Price VH, Hordinsky MK, Olsen et al. Subcutaneous efalizumab is not effective in the treatment of alopecia areata. J Am Acad Dermatol 2008;58(3):395-402.

34. Olsen EA, Whiting DA, Savin R et al. Global photographic assessment of men age 18 to 60 years with male pattern hair loss receiving finasteride 1 mg or placebo. J Am Acad Dermatol 2012;67:379-386.

35. Dolte KS, Girman CJ, Hartmaier S, Roberts J, Bergfeld W, Waldstreicher J. Development of a health-related quality of life questionnaire for women with androgenetic alopecia. Clin Exp Dermatol 2000;25:637-642.

36. Chren M-M, Lasek RJ, Sahay AP, Sands LP. Measurement properties of Skindex-16: a brief Quality -of-Life measure for patients with skin disease. J Cut Med Surg 2001;5:105-110.

37. Picardi A, Abeni D, Pasquini P. Assessing psychological distress in patients with skin diseases: reliability, validity and factor structure of the GHQ-12. J Eur Acad Dermatol Venerol 2001;15:410-417.

38. Williamson D, Gonzalez M, Finlay AY. The effect of hair loss on quality of life. J Eur Acad Dermatol Venerol 2001;15:137-139.

39. Mendoza TR, Osei JS, Shi Q, Duvic A. Development of the Alopecia Areata Symptom Impact Scale. J Investig Dermatol Symp Proceed 2013;16:S51-S52.

Figure legends:

Figure 1. SALT I visual aid[26] and computation of SALT score.

The percentage terminal hair loss in the top of the scalp is determined and multiplied by 40/100 (A), the % hair loss in the back of the scalp is determined and multiplied by 24/100 (B), the % hair loss on the left side of the scalp is determined and multiplied by 18/100 (C), and the % hair loss on the right side of the scalp is determined and multiplied by 18/100 (D). A +B +C + D = SALT score.

Figure 2. modified SALT II Visual Aid[29] and computation of ALODEX score

Density is assigned for each 1% scalp area. The density scale utilized here of 0-10 is related to percent terminal hair loss where 100% hair loss =10, 90% =9, 80% = 8, 70% = 7, 60% =6, 50% =5, 40% =4, 30% = 3, 20% = 2, 10% = 1 and no hair loss = 0. The density assignments in each of the 1% scalp areas in a given quadrant are added together and divided by maximum grade of hair loss (10) to give the % hair loss for that quadrant. The score in each quadrant is then added together to give the ALODEX score.

Figure 3. Determination of ALODEX in a representive patient.

28% (A) + 22% (B) + 18% (C) + 18% (D) hair loss = 86% scalp hair loss or ALODEX score. Please note that the scattered terminal hairs in a given area have been counted as 100% loss since that is the closest estimated percentage density using the current density scale.

The SALT score for the same patient is 28% (A) + 22% (B) + 17% (C) + 17% (D) = 84% total scalp hair loss.

Figure 4. Lesional Area and Density (LAD) score calculation.

If using the LAD score for the determination of response to a given treatment, for example in the assessment of response to intralesional steroids, it is best if the area(s) of alopecia chosen to track is clearly demarcated from the surrounding hair as shown in Figure 4A. If the margins of the areas are

instead less clear, as in A and B of Figure 4B, then one should consider marking the edges of the alopecic patch directly on the scalp and taking a representative photograph so that there is a record of what margins were used at the initial assessment. The area of each patch is determined by multiplying the long axis by its perpendicular axis. If the patch of alopecia is totally circular, πr^2 may be used instead. This method will require determining ways of identifying these areas of alopecia on subsequent visits (landmarks, photographs and/or tattoos).

Target area A= 4 cm diameter circular patch of alopecia with an area of $\pi r^2 = 3.1416 \times (4/2)^2 \times = 12.57$ cm^2. The density of this area = 90% hair loss. Area x density = 12.57 x 90/100 = 11.31 LAD score.

Target area B= 3 cm x 2.5 cm patch of alopecia with an area of 7.5 cm^2. The density of this area = 98% hair loss. Area x density = 7.5 x 98/100 = 7.35 LAD score.

Overall LAD score= A + B = 11.31 + 7.35 = 18.66

Table I: Potential negative prognostic factors in alopecia areata

1. Childhood onset (ages <6, <10, ≤14, ≤16 years old or prepuberty variously noted)[9-19] is a negative prognostic factor
2. Duration of active disease.[9,14,15,20] An episode of hair loss is defined as the onset of at least one bald patch of hair loss in the scalp or biopsy documented diffuse AA until scalp hair growth returns to baseline. The potential for full regrowth is approximately 50% at one year, 9% at 2 years, 5% at 3 years and 2% at 5 years.[9]
3. Total duration of each treatment for hair loss.[17] Treatments are often not used for a sufficient period of time to assess efficacy.
4. Prior and/or current atopy including atopic dermatitis, asthma, hay fever/allergic rhinitis, and/or allergic conjunctivitis.[11,18]
5. Family history of AA.[11,21]
6. Type 1 diabetes and other autoimmune disorders such as celiac disease and rheumatoid arthritis have been shown to have a genetic relationship to AA.[22]
7. History and extent of other hair loss conditions such as telogen effluvium and pattern hair loss can confound response to treatment of AA.
8. Nail involvement may be indicative of severity of AA.[15,19,23]

Table II. SBN Classification of Alopecia Areata

Scalp hair loss (terminal hair only):

- S_0: no hair loss
- S_1: 1-24% hair loss
- S_2: 25-49% hair loss
- S_3: 50-74% hair loss
- S_4: 75-99% % hair loss
    - S_{4A}: 75-90% hair loss
    - S_{4B}: 91-99% hair loss
- S_5: 100% hair loss

Body hair loss:

- B_0: no body hair loss
- B_1: some body hair loss
- B_2: total body hair loss

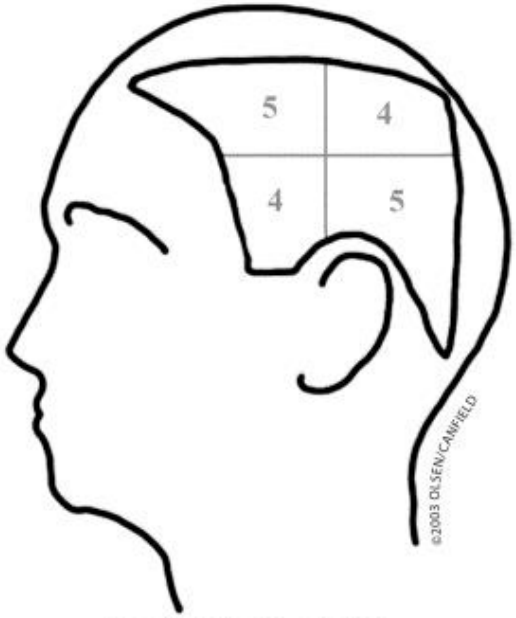
Nail involvement:

- N_0: all 20 nails do not show pitting or trachonychia
- N_1: some of nails show pitting or trachonychia
- N_2: all 20 nails show dense* pitting or trachonychia
    - N_{2A}: All nails show dense pitting
    - N_{2B}: All nails show trachonychia (“20 nail dystrophy”)

*dense is defined as at least 2 pits per nail

Table III: Methods of assessment for potential use in alopecia areata

Method	Measures	Study use	Clinic use	Comments
SALT score	% scalp baldness	X	X	By visualization, no way of documenting specific areas of hair loss
ALODEX Score	% scalp baldness	X	X	Requires use of iPAD app or too time consuming
ALODEX Tool	% scalp baldness, % scalp with any hair loss, areas of hair loss	X	X	Requires use of iPAD app. Documents areas of hair loss and density in each
AA Progressive Index	% severity of hair loss	X		Must also do/record hair pull and dermatoscopic exam findings
Half head assessment	% hair loss treated vs untreated scalp	X		Topical medications only. Best for >50% loss at BL
Lesional size of target areas	Area of several target areas	X		Best for local treatment to selected areas such IL steroids. May be difficult to select margins of hair loss
LAD score	Combines area and density of several target areas	X		Best for local treatment to selected areas such IL steroids. May be difficult to select margins of hair loss
Hair pigmentation	Pigmented vs unpigmented	X		Interest only until proven of prognostic significance
Vellus hair	Vellus only vs terminal hair	X		Interest only until proven of prognostic significance
Misc signs of hair loss	Hair pull, exclamation point hairs, dermatoscopic findings typical of AA	X		Interest only although signifies active hair loss if present
Patient assessment of extent of hair loss	Either categorization by % hair loss or S_0-S_5 AA categories	X	X	Useful for understanding patient expectations
Quality of life assessments	Several that can be utilized	X		Determines impact of hair loss on patient's life
Photographic documentation	Standardized photos of scalp hair	X	X	Corroborates response to therapy



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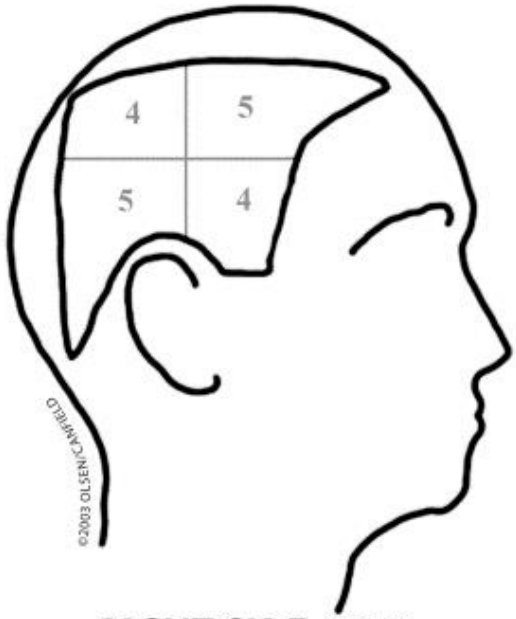

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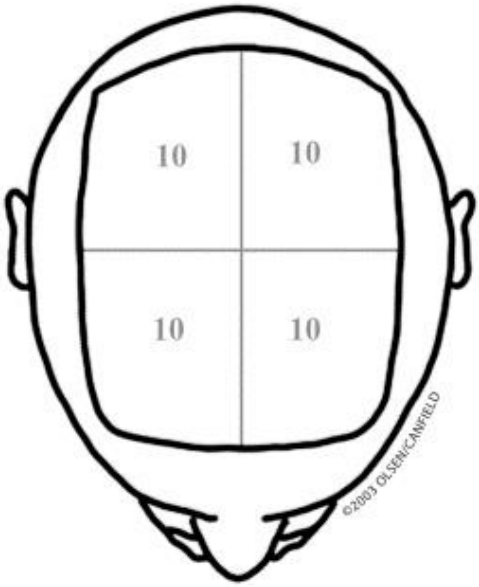

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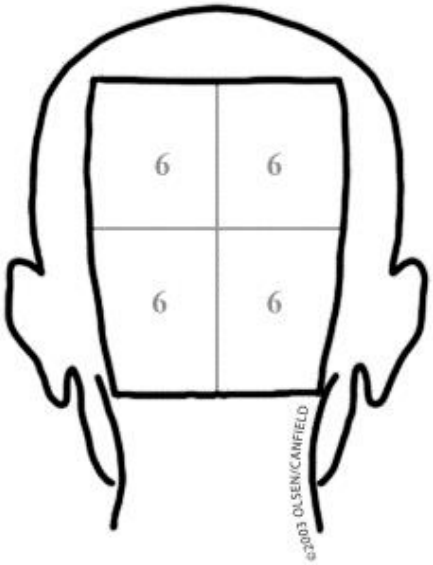

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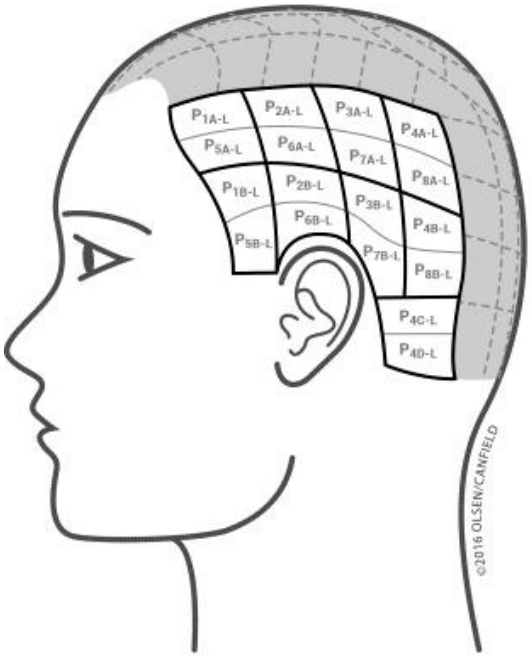

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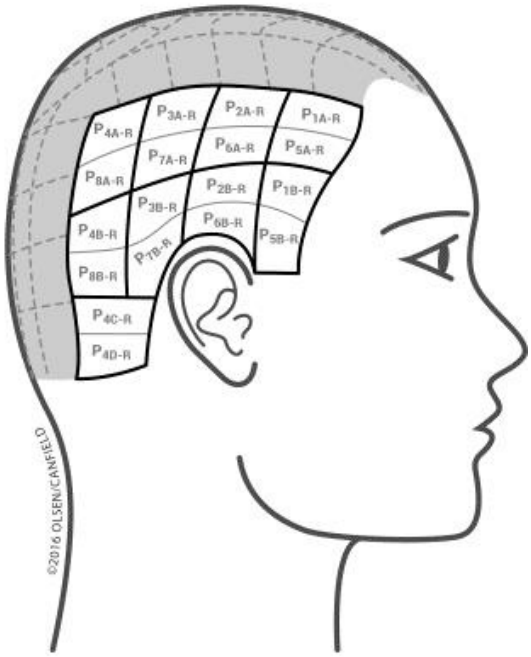

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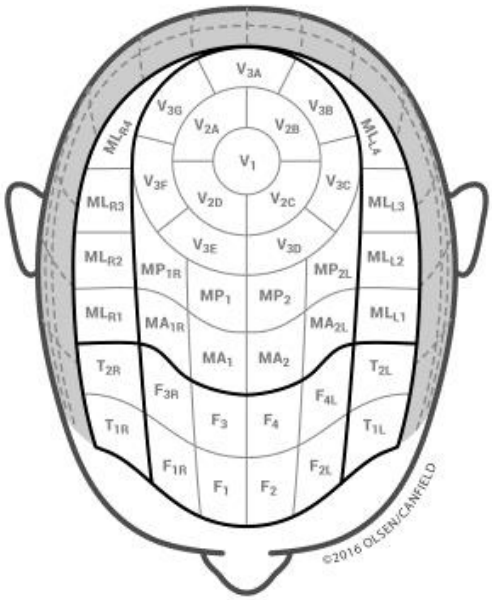

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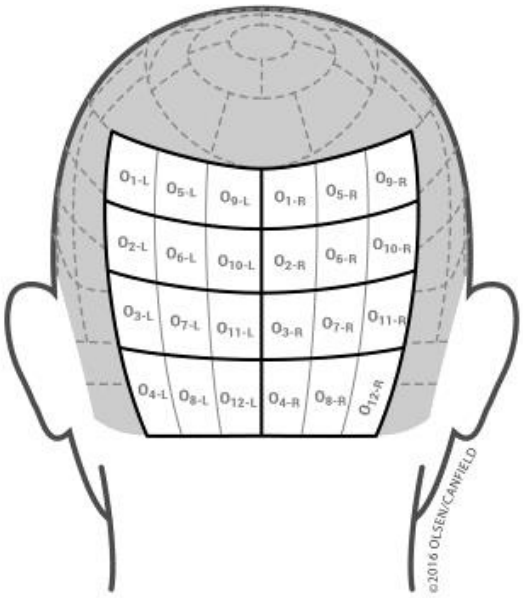

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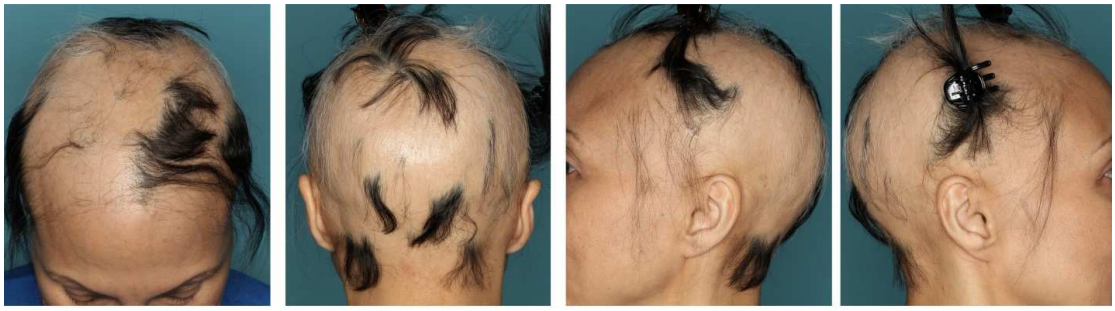
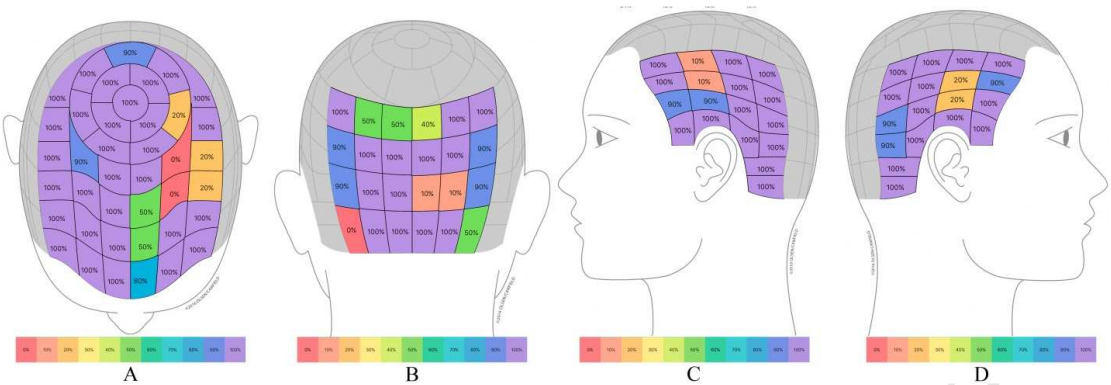


A B C D



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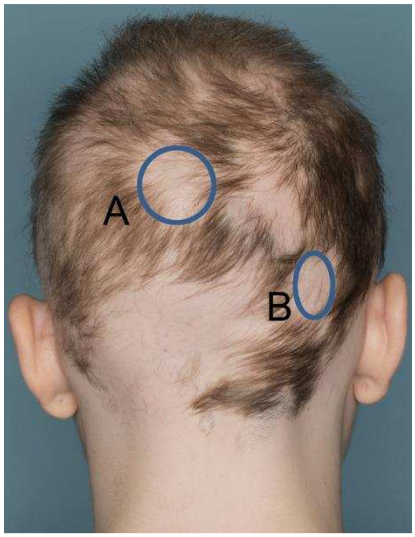

Supplemental Table IA. Initial visit of patient with alopecia areata

I. History
- A. Name: _____
- B. Date: _____
- C. Date of birth: _____
- D. Race: _____
- E. Sex: _____
- F. Age of first episode of hair loss: ___. Full regrowth? (yes/no)
- G. Subsequent episodes of hair loss? Yes/no. If yes, how many? ____
- H. Approximate age and/or dates of last 3 episodes:
  1. Episode 2: _____
  2. Episode 3: _____
  3. Episode 4: _____
- I. What is the longest period of time that you have had an episode with any amount of hair loss? _____ month or years
- J. Family history of alopecia areata (yes/no). If yes, in what members and how extensive as their hair loss [please put number next to family member (1) AT/AU or (2). patchy)]
  1. Mother: ___
  2. Father: ___
  3. Brother: ___
  4. Sister: ___
  5. Grandmother (circle Mat or Pat): ___
  6. Grandfather (circle Mat or Pat): ___
  7. Other_____
- K. Concurrent medical problems:
  1. Thyroid disease (yes/no). If yes, hyperthyroid (yes/no); hypothyroid (yes/no)
  2. Iron deficiency (yes/no)
  3. Diabetes (yes/ no). If yes, please circle how controlled: diet controlled, oral medication controlled, insulin required.
  4. Celiac disease (yes/no)
  5. Rheumatoid arthritis (yes/no)
  6. Other autoimmune diseases, personal and family_____
     _____
     _____
- L. History of: asthma (yes/no), hayfever (yes/no), atopic dermatitis or eczema (yes/no), allergic rhinitis (yes/no), family history of these conditions (yes/no)
- M. Prior and current treatments for current episode of hair loss. Response may be patient reported if no physician assessment performed and noted as none, some or complete regrowth.
  1. Treatment: _____Date started_____ Date stopped_____
     Dose or frequency of injections_____Response_____
     Any adverse effect_____
  2. Treatment: _____Date started_____ Date stopped_____
     Dose or frequency of injections_____Response_____
     Any adverse effect_____
  3. Treatment: _____Date started_____ Date stopped_____
     Dose or frequency of injections_____Response_____
     Any adverse effect_____

4. Treatment: _____Date started_____ Date stopped_____
   Dose or frequency of injections_____Response_____
   Any adverse effect_____

II. Physical Exam:

A. SALT score (see figure to record each area):_____
B. SBN categorization: _____
   A. Scalp (S): The hair loss pertains only to terminal hair and excludes vellus hair
      a. (S_0): 0-24%
      b. (S_1): 25-49%
      c. (S_2): 50-74%
      d. (S_3): 75-99%
      e. (S_{4a}): 76-95%
      f. (S_{4b}): 96-99%
      g. (S_5): 100% scalp hair loss
      h. Any vellus hair growth (yes/no). If yes, what % scalp covered_____
   B. Body hair loss (B):
      a. (B_0): none
      b. (B_1): some
      c. (B2): total
   C. Nails (N)
      a. (N_0): no involvement
      b. (N_1): some involvement
      c. (N_2): a: all 20 nails show dense* pitting
         b. all 20 nails show trachonychia (20 nail dystrophy)
C. Activity of hair loss:
   a. Exclamation point hairs: yes/no
   b. Hair pull: positive yes/no
      i. Anagen hairs: yes/no
      ii. Telogen hairs: yes/no
D. Color of hair
   a. Natural color _____
   b. Current hair growth: ___% natural color ____ % unpigmented
E. Lesional assessment for those wanting to assess local therapy in target area(s)
   a. Area of target areas: Long diameter___ x perpendicular diameter ___ = area_____ cm^2
      or for circular areas, πr^2 = area_____ cm^2
   b. Hair density in area based on 0-100 numerical number representing hair loss
   c. LAD = area x density = _____

Supplemental Table IB. Return visit of patient with alopecia areata

I. History
   A. Name: _____
   B. Date: _____
   C. Date of birth: _____
   D. Treatment:
      1. Current Treatment: _____Date started_____ Date stopped_____ Dose or frequency of injections_____Response_____
         Any adverse effect_____

2. Current Treatment: _____Date started_____ Date stopped_____ Dose or frequency of injections_____Response_____
   Any adverse effect_____
3. Current Treatment: _____Date started_____ Date stopped_____ Dose or frequency of injections_____Response_____
   Any adverse effect_____

II. Physical exam:
   A. SALT score (see figure to record each area):_____
      1. Change in SALT score= BL SALT-SALT today/SALT BL x 100 = _____
   B. Color of regrowing hair: natural color (yes/no), white (yes/no), mixed (yes/no)
   C. Vellus hair growth (yes/no). If yes, % of scalp covered_____
   D. Signs of active loss:
      1. Exclamation point hairs: yes/no
      2. Hair pull: positive yes/no
         a. Anagen hairs: yes/no
         b. Telogen hairs: yes/no
   E. Lesional assessment (LAD score) for those wanting to assess local therapy in target area(s)
      1. Long diameter___ x perpendicular diameter ___ = area_____
      2. Hair density in area based on 0-100 numerical number representing hair loss
      3. LAD = area x density = _____
      4. Change in LAD = LAD BL-LAD today/LAD BL x 100=_____

*dense is defined as at least 2 pits per nail