British Association of Dermatologists living guideline for managing people with alopecia areata 2024

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***Footnote:** This is a living guideline prepared for the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines subcommittee. Members of the Clinical Standards Unit who have been involved are S. L. Chua (Chair, Therapy & Guidelines Subcommittee), W. Gorav, R. Ramessur, M. Hashme (Information Scientist), S. Tawfik (Guideline Research Fellow), L. S. Exton (Senior Guideline Research Fellow), A. M. Constantin (Guideline Research Fellow), M. F. Mohd Mustapa (Director of Clinical Standards).

1.0 PURPOSE AND SCOPE

The overall objective of the current iteration of this living guideline is to provide up-to-date, evidence-based recommendations for the management of alopecia areata (AA) in adults (≥18 years of age), children (0-12 years of age) and young people (13-17 years of age). The document aims to:

- offer an appraisal of all relevant literature up to 19 October 2023, focusing on any key developments
- address important, practical clinical questions relating to the primary guideline objective
- provide guideline recommendations and, if appropriate, research recommendations.

The guideline is presented as a detailed review with highlighted recommendations for practical use in all appropriate community and hospital settings (see section 3.0), in addition to a Patient Information Leaflet (PIL; available on the BAD website: www.skinhealthinfo.org.uk).

2.0 METHODOLOGY

This guideline has been developed using the BAD's recommended methodology.[1] Further information can be found in Appendix K (see Supporting Information) with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument [www.agreetrust.org][2] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[3] (Appendix D, Supporting Information). Whilst the recommendations were developed for anticipated implementation in the UK National Health Service (NHS), they could equally be adapted in other healthcare systems, internationally, acknowledging different countries' health systems, including their priorities, legislation, drug availabilities, funding and policies.

The guideline development group (GDG) consisted of eight consultant dermatologists (MJH; PF; SH; VMLJ; AK; AEM; AGM; AT), three dermatology specialist registrars (AA; LA; GH), one consultant clinical psychologist (ART), two patient representatives (AJ; AN) and a technical team (consisting of an information scientist (MH), two guideline research fellows (LM; AMC) and a project manager (MFMM) providing methodological and technical support).

The GDG established one systematic review question pertinent to the scope of the guideline and a set of outcome measures of importance to patients, ranked according to the GRADE methodology[4] (section 2.1 and Appendix A; see Supporting Information).

A systematic literature search of MEDLINE, EMBASE and Cochrane databases was conducted by the technical team to identify key articles pertaining to AA up to 19 October 2023; the search terms and the search strategies are detailed in the Supporting Information (Appendix L). Additional references relevant to the topic were also isolated from citations in reviewed literature. Data extraction and critical appraisal, data synthesis, evidence summaries, lists of excluded studies and the Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram were prepared by the technical team. The overall certainty of evidence from the studies included in the quantitative review was graded according to the GRADE system (high, moderate, low or very low certainty).

In making these recommendations, all GDG members have evaluated the entire data set obtained from the living systematic review of the literature pertaining to the clinical question of interest (section 2.1).

The recommendations were formulated following discussions with the entire GDG, including patient representatives, considering all factors that would affect the strength of the evidence according to the GRADE approach (i.e. balance between desirable and undesirable effects, quality of evidence, patient values and preferences and resource allocation). All GDG members contributed towards drafting and/or reviewing the narratives and information in the guideline and appendices in the supporting information documents. When insufficient evidence from the literature was available, informal consensus was reached based on the experience of the GDG.

The summary of findings with forest plots (Appendix B), tables Linking the Evidence To the Recommendations (LETR) (Appendix C), GRADE evidence profiles indicating the certainty of the evidence (Appendix D), summary of comparative studies included in the quantitative and qualitative synthesis (Appendix E), summary of included within-patient studies (Appendix F) narrative findings from non-comparative studies (Appendix G), PRISMA flow diagram (Appendix H), risk of bias analysis (Appendix I) and the list of excluded studies (Appendix J) are detailed in the Supporting Information.

The strength of recommendation is expressed by the wording and symbols as shown in Table 1.

Applicability of the recommendations to clinical practice is outlined in sections 4.0 and 7.0. A 'patient values and preferences' section and further discussion of the included evidence, treatment options, practical and economic considerations, service provision, etc. is also featured in the LETR narrative (Appendix C; see Supporting Information).

2.1 Clinical questions and outcomes

The GDG established a systematic review question pertinent to the scope of the guideline. See Supporting Information (Appendix A) for the full living systematic review protocol.

The GDG also established a set of outcome measures of importance to people with AA, which were agreed by the patient representatives and ranked according to the GRADE methodology.[4] Outcomes ranked 7, 8 or 9 are critical for decision making; those ranked 4, 5 or 6 are important, but not critical for decision making; and those ranked 1, 2 or 3 are the least important for decision making.

Systematic review question: In people with AA what is the clinical effectiveness and safety of interventions compared with each other, placebo or no treatment?

Outcomes:

Critical

- Improvement in quality of life and psychological well-being (anxiety/social anxiety/ depression) **(9)**
- Improvement in hair regrowth from baseline (e.g. ≥75%)* **(8)**
- Improvement in facial (i.e. eyelash, eyebrow, beard) hair regrowth from baseline **(8)**
- Serious adverse effects (i.e. Grades 3-4 adverse events, investigator-defined) **(8)**
- Long-term sustainability of hair regrowth **(8)**

Important

- Patient's self-assessment **(6)**
- Disease-specific physician's assessment **(6)**
- Improvement in hair regrowth from baseline (e.g. ≥50%) **(6)**
- Physician's global assessment **(6)**
- Minor adverse effects (i.e. Grades 1-2 adverse events) **(5)**

Less important

- Improvement in hair regrowth from baseline (e.g. ≥25%) **(3)**

*Where reported, data on 90-100% improvement of hair regrowth from baseline are to be extracted additionally and separately.

3.0 SUMMARY OF RECOMMENDATIONS

The GDG set out to provide an up-to-date and evidence-based approach to optimise the management of people with AA, factoring in patient values and preferences.

The following recommendations and ratings were agreed upon unanimously by all members of the GDG, including patient representatives. For further information on the wording used for

recommendations and strength of recommendation ratings see section 2.0. The GDG is aware of the lack of high-certainty evidence for some of these recommendations, therefore strong recommendations with an asterisk (*) are based on available evidence, as well as consensus and specialist experience. Good practice point (GPP) recommendations are derived from informal consensus.

The GDG considered the evidence and provided recommendations in the context of clinical practice within the UK's NHS. However, the GDG acknowledged that some recommended interventions may not be widely available. The evidence for recommendations is based on the studies listed. For further details please refer to the discussion in the LETR (Appendix C; see Supporting Information).

All recommendations which employ the term 'people' refer to ***adults***, ***children*** and ***young people***. The terms 'male' and 'female' used throughout the guidelines refer to the sex assigned at birth.

The AA severity definitions used in these guidelines are based primarily on extent of scalp hair loss, with ***limited (mild)*** hair loss representing 1-20% scalp involvement, ***moderate*** hair loss representing 21-49% scalp involvement and ***severe*** hair loss representing 50-100% scalp involvement.[5] However, this severity grading should be increased if additional clinical features are present (see section 6.2). ***Rapidly progressive*** AA is defined here as progressive scalp hair loss of sudden onset, associated with increased hair fall and generalised positive hair pull test and/or trichoscopic features of active disease (e.g., exclamation mark hairs, black dots, etc.).[6]

The definitions of psychological distress used in these guidelines should be based on the outcome of clinical assessment and judgement. However, this can be supported by the use of mental health patient reported outcome measures or screening tools (PROMs; see Appendix O) that have psychometrically reliable cut-off points.

General management

R1 (GPP) Undertake a full history for people with AA, including site and type of AA, disease extent, disease stability, age of onset, speed of progression, triggering factors, quality of life, psychological and psychosocial impact, maximum severity experience and personal and family history of other autoimmune diseases.

R2 (GPP) Manage the expectations of people with AA by conveying that any therapeutic modality is not always effective.

R3 (GPP) Offer all people with AA medical photography[7] as a baseline record of severity and consider further photography if there is a significant change and at the start of a new treatment course.

R4 (GPP) Perform the Severity of Alopecia Tool (SALT) assessment (see Appendix N, Supporting Information) routinely in people with AA with scalp involvement as a validated outcome measure to assess treatment response over time.

R5 (GPP) Exercise caution when treating people with AA with Fitzpatrick V and VI skin tones with topical and/or intralesional corticosteroids and contact immunotherapy, due to the increased risk of skin depigmentation with corticosteroid treatment and the risk of developing vitiligo, as well as localised skin hyper- or hypopigmentation, with contact immunotherapy. These patients need specific counselling prior to treatment regarding potential skin pigmentary changes.

R6 (↑↑) Assess* and monitor people's quality of life and level of psychological distress associated with living with AA. Brief screening tools that can be used include Patient Health Questionnaire-4 (PHQ-4)[8] or Patient Health Questionnaire-9 (PHQ-9),[9,10] Generalized Anxiety Disorder 7 (GAD7),[11] Mood and Feelings Questionnaire – short (MFQ(S)[12] and Dermatology Life Quality Index (DLQI).[13] Disease-specific measures include the Alopecia Areata Symptom Impact Scale (AASIS)[14] and Alopecia Areata Patient Priority Outcome (AAPPO).[15]

R7 (GPP) Discuss with people with AA the psychosocial impact of living with the condition.

R8 (GPP) Provide people with AA, at the time of diagnosis, with a patient information leaflet (PIL; e.g. https://www.skinhealthinfo.org.uk/condition/alopecia-areata), actively engage them in their treatment management pathway to facilitate shared decision-making, and direct them to appropriate patient support organisations (e.g. Alopecia UK).

R9 (GPP) Offer people with AA the opportunity to participate in a long-term safety registry [e.g. the Global Registry of Alopecia areata disease Severity and treatment Safety (GRASS-UK; www.bad.org.uk/research-journals/research/grass-uk/)].

R10 (GPP) Refer people with suspected AA to a healthcare professional experienced in managing the condition (secondary care specialist or general physician with enhanced role, GPwER) if:

- the condition is severe
- the condition is progressing rapidly
- there is diagnostic uncertainty
- the condition has a significant psychosocial impact, or
- the condition is not responding to topical treatment.

Further advice on referral pathways can be found on the British Association of Dermatologists website page: 'Dermatology Referral Management Guidelines' (www.bad.org.uk/referrals/) which provide an

accessible national clinical resource intended to support clinicians in primary, community and secondary care services.

Wigs and other non-pharmacological therapies

R11 (↑↑) Offer wigs (including toppers) to people with AA whose quality of life is likely to benefit from their use. Due to the lifespan of products, it is suggested that patients are offered a minimum of two synthetic wigs or one human hair wig (if meeting clinical criteria), per year in accordance with the Charter for Best Practice for NHS Wig Provision.[16]

R12 (GPP) Acknowledge that wigs and other non-pharmacological therapies can be as significant in improving patient quality of life as other treatments.

R13 (GPP) Suggest that people with AA explore other headwear and camouflage options, such as hats, scarves, turbans, make-up, hair fibres, powders and sprays, permanent make-up and skin micropigmentation. The national hair loss charity, Alopecia UK, has comprehensive information about products and services on its website (www.alopecia.org.uk).

Topical corticosteroids

R14 (↑↑) Offer* a potent or very potent topical corticosteroid once daily for 3-6 months to ***people*** with AA who have ***scalp*** hair loss, as the first-line treatment in primary or secondary care.

R15 (↑) Consider a potent or very potent topical corticosteroids treatment regimen of 6 weeks' treatment and 6 weeks' break, followed by a further 6 weeks' treatment cycle in ***children and young people*** with ***scalp*** AA.

R16 (GPP) Discuss with people with AA the amount of topical corticosteroids to be used, the site of application and the safety of a potent or very potent topical corticosteroid when used correctly.

R17 (GPP) Reassess the use of topical corticosteroids every 3-6 months in people with AA, to assess for improvement and cutaneous side effects.

Intralesional corticosteroids

R18 (↑↑) Offer* intralesional triamcinolone acetonide (2.5–10 mg/ml) as a first-line option to ***adults*** with ***limited (mild)-to-moderate*** AA.

R19 (↑) Consider intralesional triamcinolone acetonide in ***adults*** with ***severe*** AA on a case-by-case basis.

R20 (↑) Consider intralesional triamcinolone acetonide in ***older children and young people*** with ***limited (mild)-to-moderate*** AA on a case-by-case basis.

R21 (↑) Consider intralesional triamcinolone acetonide in people with eyebrows or beard alopecia on a case-by-case basis.

R22 (GPP) Exercise caution when treating people with AA with intralesional corticosteroids due to risk of localised skin or fat atrophy, particularly when treating cosmetically sensitive sites or if previous episodes of atrophy have occurred.

R23 (GPP) Consider initial starting concentration of 5 mg/ml for intralesional triamcinolone acetonide as standard practice in all ***adults*** with AA. Adjusted concentrations may be required depending on response or risk of side effects.

R24 (GPP) Consider a time interval of 6-12 weeks for intralesional triamcinolone acetonide injections for people with AA and ensure that the injections are evenly spaced within the patch and patch margins (i.e. 0.1 ml/1 cm^2).

R25 (GPP) Consider options (e.g. topical local anaesthetics, cold-spray or distraction/vibration) to reduce pain when injecting intralesional triamcinolone acetonide in people with AA.

Systemic corticosteroids

R26 (↑) Consider a course of oral corticosteroid (e.g. prednisolone 0.5 mg/kg/day tapering over 6-12 weeks) in people with ***rapidly progressive*** AA. Intravenous methylprednisolone 500 mg daily for 3 days may be an alternative to oral corticosteroids in adults, although this treatment is not used widely in the UK.

R27 (↑) Consider a course of oral corticosteroid (e.g. prednisolone 0.5 mg/kg/day tapering over 6-12 weeks) in people with ***moderate-to-severe*** AA.

R28 (↑) Consider concurrent topical treatment (e.g. potent topical corticosteroid, 5% minoxidil topical solution) in people with ***moderate-to-severe*** AA, to reduce the risk of relapse. Taper corticosteroid use over 6-12 weeks with the aim of maintaining response thereafter with the topical agent.

R29 (↑) Consider concurrent treatment with corticosteroid-sparing agents (e.g. azathioprine, methotrexate, ciclosporin) in people with ***moderate-to-severe*** AA, to reduce the risk of relapse. Taper corticosteroid use over 6-12 weeks with the aim of maintaining response thereafter with the steroid-sparing agent.

R30 (GPP) Acknowledge that some people treated with oral corticosteroids may be unable to maintain a treatment response as the dose is reduced or stopped. The side effect profile of oral corticosteroids usually precludes longer term maintenance therapy, particularly if higher doses are required to maintain an effect.

Contact immunotherapy

R31 (↑↑) Offer diphenylcyclopropenone (DPCP), where available, to people with ***moderate-to-severe*** AA.

R32 (↑) Consider "home DPCP" (where available, under hospital guidance) in people with AA who can conduct the procedure correctly and safely at home, for their easy access and convenience.

R33 (↑↑) Use DPCP or squaric acid dibutyl ester (SADBE) as a sensitising agent in people with AA.

R34 (↓↓) Do not use dinitrochlorobenzene (DNCB) as a sensitising agent in people with AA due to the risk of mutagenicity.

Light and laser

R35 (↑) Consider topical and oral PUVA in people with AA in selected cases depending on the risk/benefit ratio. For example, this option may be more acceptable in people with darker skin tones (e.g. Fitzpatrick V and IV) who would like a localised treatment option and avoid the risk of skin depigmentation with topical immunotherapy. If used, consider shorter treatment cycles, application to smaller areas and a finite treatment duration.

Θ There is insufficient evidence to recommend the following light and laser interventions to people with AA:

- narrowband ultraviolet B (NB-UVB)
- ultraviolet-A1 (UVA1)
- laser-assisted delivery of topical agents (such as minoxidil and corticosteroids) with fractioned, ablative CO_2 laser or fractionated non-ablative erbium laser
- low-level light laser therapy (LLLT) devices
- pulsed infrared diode laser
- photodynamic therapy (PDT)
- Nd:YAG laser
- excimer lamp
- other laser treatments (e.g. 311-nm Titanium: Sapphire laser, nonablative 1,550 nm erbium glass fractional laser; Ablative fractional 2940-nm erbium:yttrium-aluminum-garnet (Er:YAG) laser).

Systemic immunosuppression

R36 (↑) Consider ciclosporin, azathioprine or methotrexate as monotherapy or in combination with oral corticosteroids as treatment options in people with ***moderate-to-severe*** AA, balancing benefits and risks of adverse effects and patient risk factors.

R37 (GPP) Consider mycophenolate mofetil in adults with ***moderate-to-severe*** AA, balancing benefits and risks of adverse effects and patient risk factors.

R38 (GPP) Consider ciclosporin in people with ***rapidly progressive*** AA for a limited course (i.e. 3 - 6 months), to encourage initial hair regrowth.

Other systemic treatments

ϴ There is insufficient evidence to recommend the following systemic interventions to people with AA:

- inosiplex (isoprinosine or inosine pranobex)
- imipramine
- apremilast
- sulfasalazine
- mesalazine
- hydroxychloroquine
- dimethyl fumarate.

Janus kinase inhibitors

R39 (↑↑) Offer a licensed oral Janus kinase inhibitor (if available) to ***adults*** with ***severe*** AA.

R40 (↑↑) Offer a licensed oral Janus kinase inhibitor (if available) to ***young people*** with ***severe*** AA.

R41 (GPP) Discuss the recent drug safety update issued by the Medicines and Healthcare products Regulatory Agency (MHRA),[17] 'Black Box' warning by the Food and Drug Administration (FDA)[18] or safety recommendation by the European Medicines Agency (EMA)[19] regarding increased risk of venous thromboembolism (VTE), serious cardiovascular events, cancer and death with Janus kinase inhibitors. These drugs should be prescribed with caution in anyone over 65 years old or with risk factors for these conditions.

ϴ There is insufficient evidence to recommend topical Janus kinase inhibitors to people with AA.

Biologics

R42 (↓↓) Do not offer efalizumab to people with AA, as the evidence shows that it is ineffective in this population and the risk of adverse events may exceed any potential benefit.

ϴ There is insufficient evidence to recommend the following biologic interventions to people with AA:

- ustekinumab
- secukinumab
- abatacept
- intramuscular alefacept
- tumour necrosis factor-alpha inhibitors
- low-dose anti-interleukin-2
- dupilumab.

Other topical treatments

R43 (↑) Consider topical dithranol (if available) as a treatment option in people with AA, especially in children and young people or those with lack of access to DPCP. Advise patients about staining properties of dithranol, which can affect scalp hair, fabric and other materials.

R44 (GPP) Consider topical prostaglandin analogues (application only on the upper eye lid margin) in ***adults*** with eyelash alopecia when some hair presence or signs of hair regrowth exists. These agents are probably ineffective at restoring growth where hair has been fully lost. Counsel patients regarding the risk of permanent increased pigmentation of the iris.

ϴ There is insufficient evidence to recommend the following topical interventions to people with AA:

- calcineurin inhibitors
- calcipotriol
- ciclosporin
- azelaic acid
- methotrexate 1% gel
- tretinoin
- prostaglandin analogues for scalp alopecia
- dithranol in combination with contact immunotherapy
- dithranol in combination with salicylic acid and coal tar
- mechloretharnine hydrochloride (nitrogen mustard)
- diclofenac sodium
- liquid phenol
- 5-fluorouracil
- sildenafil.

Minoxidil

R45 (GPP) Consider topical or oral minoxidil in people with AA as an adjuvant to other treatment modalities, as it can improve hair density and may reduce the possibility of relapse.

Psychological

R46 (↑↑) Offer* information on self-help and patient support (e.g. leaflets, books, websites, apps) to people with ***mild*** psychological distress. General recommendations on treatment and management of low mood are available in NICE guidelines NG222[20] and NG134.[21]

R47 (↑↑) Offer* referral for formal psychological intervention (including individual or group cognitive behavioural therapy (CBT) and specialised forms of CBT that include mindfulness) to people experiencing ***moderate-to-severe*** psychological distress.

R48 (↑↑) Offer* the use of psychotropic medication (under the supervision of a suitably trained clinician) or/and referral for more intensive forms of psychological therapy or psychiatric intervention, for ***more severe*** psychological distress.

R49 (GPP) When indicated, formally assess for risk of suicide. Recommendations on brief assessment of suicide risk are available on the NHS England e-learning platform and NICE guideline NG225.[22]

Other non-steroid injectable therapies

Θ There is insufficient evidence to recommend the following injectable interventions to people with AA:

- platelet-rich plasma (PRP)
- micro-needling
- carboxytherapy
- cryotherapy
- intralesional pentoxifylline
- intralesional methotrexate
- intralesional vitamin D
- mesenchymal stem cells
- intralesional interferon alfa
- intradermal minoxidil.

Alternative therapy

Θ There is insufficient evidence to recommend the following alternative interventions to people with AA:

- aromatherapy
- allium/onion ointment

- ginseng
- paeony
- glycyrrhizin
- combined complimentary therapies (herbal, nettle, dandelion)
- poison primrose (primula obconica)
- herbal sensitisers
- candida antigen
- squill lotion
- hypnosis.

Future research recommendations

The following list outlines future research recommendations (FRRs).

FRR1 Randomized controlled trials to evaluate the safety and efficacy of oral JAK inhibitors compared with commonly used interventions in people with AA.

FRR2 Clinical trials evaluating investigational medicinal products (IMPs) in people with AA should also report on psychological outcomes, using appropriate measurement scales for AA.

FRR3 Development of an international core outcomes set for AA clinical trials to permit data comparison and metanalyses.

FRR4 To study the minimal clinically important difference (MCID) for existing disease-specific tools for AA.

FRR5 Clinical trials to evaluate the effectiveness of psychological interventions and/or therapy in reducing distress associated with AA.

FRR6 Development of biomarkers and other patient stratification tools to better predict prognosis and inform treatment choices for people with AA.

FRR7 Identify the most suitable health utility tool for assessment of treatments for managing people with AA.

4.0 ALGORITHM

The recommendations, discussions in the LETR (Appendix C; see Supporting Information) and consensus specialist experience were used to inform the algorithm/pathway of care (Fig. 1).

5.0 BACKGROUND

AA is a chronic inflammatory disease that affects the hair follicles (HF) and sometimes the nails. It usually presents with patchy scalp hair loss, which can extend to involve the entire scalp, but any hair-bearing skin may be involved, including facial and body hair. Total loss of scalp hair is called *alopecia totalis* (AT) and complete loss of scalp, facial and body hair is called *alopecia universalis* (AU). The affected skin may be slightly reddened, but usually appears normal. Short broken hairs (exclamation mark hairs) are frequently seen around the margins of expanding patches of AA on trichoscopy (dermoscopy). The nails are involved in about 10% of patients referred for specialist advice.[23] A recent UK-based epidemiology study estimated the point prevalence, in 2018, of adults with AA as 0.58% and the peak age of onset as 25-29 years for both sexes. Patients of non-white ethnicity are more likely to present with AA, specifically those of Asian descent.[24]

5.1 Prognosis

The most important prognostic indicators for AA are disease severity and age at initial presentation, with extensive disease and younger age of onset predicting a poorer outcome.[25] These factors are demonstrated in an Italian study of 191 AA patients seen in clinic between 1983 and 1990 who were contacted by telephone 16-23 years later and self-reported their clinical status. Patients with mild disease (<20% scalp area affected) at presentation were more likely to report being disease-free at follow-up (68% of cases). However, there was a significant tendency for AA to worsen over time with 19% of those originally seen with mild-moderate disease (<50% scalp area affected) progressing to AT/AU at follow-up, 93% with AU still having extensive disease (AT/AU) at follow-up, and only 3% originally with extensive disease (AT/AU) being disease-free at follow-up.[26] Thus, a tendency to progressive disease, and episodes of disease relapse, are common in this condition.[27-29]

Hair follicles (HF) are preserved in AA, therefore the potential for recovery of hair growth is maintained, although recovery rates may diminish in longstanding disease. Other factors that may affect prognosis include the AA subtype, positive family history and nail disease. The ophiasis subtype (where alopecia affects the hair margins) confers a poorer prognosis and may be less responsive to treatment; however, the recently described "acute diffuse and total alopecia" subtype may have a more favourable prognosis.[30] The presence of atopy has also been shown to be associated with treatment resistance in patients with patchy AA.[29]

5.2 Aetiology

The exact pathogenesis of AA is unknown. However, AA is considered a chronic T-cell-mediated inflammatory disorder where loss of HF immune privilege, infiltration of pro-inflammatory cytokine-secreting T-cells around the hair follicle bulb, and premature catagen induction are key features in active disease and necessary for hair loss development.[31] Genetic predisposition and (as yet unidentified) environmental factors may also be relevant in disease pathogenesis.[32,33]

5.2.1 Genetic factors and autoimmune associations

Genetic predisposition seems to be one of the main determinants for developing AA, with about 20% of people having a family history of the disease.[34] Genome-wide association studies have confirmed the link with major histocompatibility complex (MHC) genes and other genes involved in regulating innate and adaptive immunity, with several of the identified AA susceptibility loci also prevalent in other autoimmune diseases.[33] The human leukocyte antigen (HLA) class II genes DR4, DR5, DQ3, DQ7 and DPW4 alleles have been strongly associated with AA susceptibility, with HLA-DR on chromosome 6 showing the greatest risk of disease development.[35] CD4+ and CD8+ T-cells have a key role in AA pathogenesis and have been linked to these HLA class II genes.[35]

There are several other pathways that have been implicated in AA pathogenesis including genes encoding natural killer cell receptor D (NKG2D) ligands MHC class I polypeptide-related sequence A (MICA) and UL16-binding protein (ULBP), that act as "danger-signals" in the HF, downstream effectors of the JAK pathway,[36] T-regulatory cell (Treg) pathways [35] and melanin-concentrating hormone signalling pathways.[37,38]

5.2.2 Hair follicles immune privilege collapse

The lower portion of the normal HF demonstrates immune privilege (a complex array of mechanisms that restrict antigen presentation from these cells),[39] meaning HFs are protected from immune surveillance by autoreactive T cells. In AA, CD8+ T cells and NKG2D+ cells target anagen hair follicles with disrupted immune privilege.[40] Increased interferon (IFN)-γ responses and upregulation of several common γ-chain (γc) cytokines, including interleukin (IL)-2, IL-7, IL-15, and IL-21, promote recruitment, activation and survival of IFN-γ-producing CD8+ NKG2D+ T cells resulting in immune privilege collapse,[41] HF dystrophy and premature entry of hairs into catagen phase, leading to the development of hair loss.[31,42]

5.2.3 Environmental factors

Emotional stress is an often-cited cause of AA based on patient-reported triggers, along with biological changes seen in mice models and human *ex vivo* hair follicle culture studies.[43-45] Other potential environmental stressors that may be implicated in AA include infections,[46] vaccinations, hormone fluctuations and diet, although their precise role is uncertain.[32] Several studies have suggested a correlation between AA severity and vitamin D deficiency; however, the role of vitamin D in AA pathogenesis remains unclear.[47,48] Gut microbiota has been shown to have a key role in influencing various inflammatory and autoimmune diseases,[49] with gut dysbiosis being a potential additional factor in AA.[50]

5.3 Comorbidities

5.3.1 Atopic and autoimmune associations

Alopecia areata has been associated with several other autoimmune and atopic disorders. A population-based cohort study of 8,051 newly diagnosed AA cases and 32,204 case-matched controls in England demonstrated that atopic and autoimmune conditions were more prevalent in AA cases than in controls, showing an increased risk of atopic dermatitis, allergic rhinitis, autoimmune hypothyroidism, systemic lupus erythematosus and vitiligo.[51] Age of AA onset may influence the relative risk of developing these conditions[52] with atopic dermatitis significantly associated with a younger age of onset.[53]

5.3.2 Anxiety and depression

The emotional and functional impact of AA is well recognised, with increased levels of both co-existing, and new-onset, anxiety and depression seen in AA cases compared with controls. Furthermore, having AA is associated with a greater likelihood of being issued time-off-work certificates or being recorded as unemployed.[54] A recent study suggests a bi-directional association between severe depression and AA, indicating that both conditions are independent risk factors for the development of the other.[55] Biologically, systemic inflammation may contribute, with serum IL-22 and IL-17E levels correlating with depression symptoms.[56] Social discrimination and/or stigmatisation is also likely to contribute.[57]

5.3.3 Increased cardiovascular risk?

Data from recent publications suggest that AA may be associated with increased cardiovascular and metabolic risk, with stroke and acute cardiac events being seen more frequently, particularly in long-standing cases.[58-60] The potential cause for this is unclear, but chronic inflammation, disease associations, smoking status and the consequence of treatments may play a role. Unfortunately, the published literature shows conflicting results,[61,62] so further work is needed to better understand these potential associations and whether risk reduction strategies are specifically needed in this patient group.

6.0 DIAGNOSIS AND INVESTIGATION

The diagnosis of AA is usually based on the clinical presentation and typical examination findings. Trichoscopy can aid diagnosis and management of AA, identifying preserved follicular ostia and regular yellow dots in areas of hair loss and exclamation-mark hairs and black dots typically seen at the hair loss margin when the disease is active. However, the following conditions may cause diagnostic difficulties and should be considered in the differential diagnosis of patchy AA.[63]

1) ***Trichotillomania*** (hair pulling disorder*)*
   Due to self-inflicted traumatic damage to the hairs as a result of recurrent pulling out of hair is characterized by irregular patchy loss with broken hairs of variable length. In contrast to AA, hairs in trichotillomania are firmly attached to the scalp.
2) ***Tinea capitis***

Patchy hair loss, particularly in children, with features of scalp inflammation and surface scale, although these signs may sometimes be subtle.

3) ***Early scarring alopecia***
Trichoscopy is useful in identifying loss of follicular ostia, along with other signs such as perifollicular erythema and perifollicular scale seen in scarring alopecia. A biopsy may be required to exclude this diagnosis.

4) ***Temporal triangular alopecia***
Typically presents in childhood with a static, non-inflammatory triangular or oval patch containing vellus hair located at the frontal hairline; sometimes the condition can be bilateral. In contrast with AA, there are no yellow dots, black dots or exclamation mark hair seen in this condition.

Occasionally, AA may present with diffuse hair loss associated with increased hair fall, but without the typical patches. Further investigation may be necessary, and the following differential diagnoses should be considered in this presentation:

1) telogen effluvium
2) anagen effluvium (drug-induced)
3) systemic lupus erythematosus
4) secondary syphilis (usually patchy and "moth-eaten").

For children presenting with complete alopecia within the first year of life, clinicians should also consider congenital conditions associated with total hair loss that may be clinically indistinguishable from AT/AU, particularly "Atrichia with papular lesions" and Vitamin D-dependent rickets.[64]

6.1. Investigations

Investigations are unnecessary in most cases of AA.[65] If there is diagnostic uncertainty (see section 6.0) appropriate testing may include fungal cultures, skin biopsy, diagnostic criteria and serology testing for systemic lupus erythematosus or syphilis screening. Investigations for co-existing autoimmune conditions should be considered on a case-by-case basis depending on the patient history and clinical presentation.

6.1.1. Thyroid disease

An association between AA and autoimmune thyroid disease has long been recognised,[66] but opinions are divided on whether routine screening of thyroid function is justified. Two meta-analyses of published data have concluded that the risk of hypo- and hyperthyroidism is significantly increased in AA.[67,68] However, a third failed to show an association with diagnosed or serological hypo- or hyperthyroidism; although there was a significant association between AA and the presence of thyroid autoantibodies which, in long term studies, have been associated with the later development of overt disease.[69] The risk of thyroid disease and of serological thyroid abnormalities appears greater in AT and

AU. [70,71] The frequency of thyroid disease is greatest in the older age groups, as it is in the population at large, but the risk (vs. that in the age-matched population) is greatest in the under 20s.[71] In a study of thyroid function in 298 children with AA the investigators concluded that routine screening in children should be restricted to those with a medical history of Down's syndrome, a history of atopy, a family history of thyroid disease or clinical features suggestive of thyroid disease.[72] Whether routine thyroid screening should be performed in adults is debatable, but it may be considered, notably in AT and AU. If performed, tests should include thyroid autoantibodies and thyroid stimulating hormone and recognise that the increased risk of thyroid disease in AA is lifelong.

6.1.2. Iron, vitamin D and other nutritional deficiencies

Deficiencies of nutrients, including iron, zinc and selenium have been linked with AA. However, these studies are small and show conflicting results. Routine testing for iron status is not supported by evidence. There are no published studies demonstrating a treatment response to iron replacement therapy.[73-76] There have been reports of decreased serum levels of vitamin D[77] and an inverse correlation with severity of AA,[48] while others have not found an association between dietary, supplemental or total vitamin D intake and incident AA.[78] Ultimately, studies are required to assess the value of vitamin D supplementation in the treatment of AA.

6.2 Severity of disease

Most recent clinical trials for AA use the Severity of Alopecia Tool (SALT) score (see Appendix N) to categorise the levels of scalp hair loss, based on percentage terminal scalp hair loss.[79,80] Severity criteria is presented in the "AA Investigator Global Assessment"[81] and "Scalp Hair Assessment PRO" tools[82] that present severity gradations of scalp alopecia for use in clinical trials, with grade 0 ("**None**"; 0% scalp loss), grade 1 ("**Limited" (Mild)**; 1-20% scalp loss), grade 2 ("**Moderate**"; 21-49% scalp loss), grade 3 ("**Severe**"; 50-94% scalp loss) and grade 4 ("**Very severe**"; 95-100% scalp loss). This severity classification can be simplified for clinical practice by combining the top two severity categories into one severity grade ("Severe") representing 50-100% scalp hair loss, as used in these guidelines. Further, validated clinician- and patient-reported outcome measures are now available to assess eyebrow, eyelash and nail involvement.[83]

Unfortunately, the extent of scalp hair loss alone does not capture the wider impact of AA on an individual, particularly when psychological distress or functional impact (e.g. loss of eyelashes or nails) is prominent or when other visible body sites are involved. Therefore, a recent expert consensus[5] has advocated adjusting the SALT-based severity rating when other additional factors are present. Thus, limited- or moderate-AA may have their severity rating increased by one level if one or more of the following are present:

- "Negative impact on psychological functioning resulting from AA" (see Appendix O)
- "Noticeable involvement of eyebrows or eyelashes"
- "Inadequate response after at least 6 months of treatment"

- "Diffuse (multifocal) positive hair pull test consistent with rapidly progressive AA".

Other factors (e.g. religious significance of hair growth) can also increase the impact of AA in certain situations.[84] This emphasises that clinical assessment of AA severity must be holistic, addressing individual patient needs and should be a priority area for future research.

7.0 MANAGEMENT

A complete history and careful clinical assessment are required in all people with suspected AA, to confirm the diagnosis and exclude conditions that may mimic this disease (see section 6.0). As part of the assessment, explore the functional and psychological impact of the condition and determine the priorities for treatment, as these may differ from person to person. A frequent example is how someone prioritizes their desire to regrow their scalp, eyebrow or beard hair over hair regrowth at other body sites, with different treatment approaches often required to achieve this priority of that individual.

Various factors (see section 6.2), in addition to affected scalp area, can influence disease severity. Discussion of the unpredictable and relapsing nature of AA is important, as that may influence which treatments are chosen. Furthermore, recognition that extensive disease (AT/AU), longer duration of disease and certain presentation (e.g. ophiasis pattern) confer a worse prognosis and reduced likelihood of a successful treatment response.

All people with AA should have a severity assessment (e.g. SALT score) and medical photography[7] at baseline, with these assessments repeated if the clinical situation changes or new therapies are considered. As treatment of AA takes time it is important that the therapeutic trial is of sufficient duration to allow a treatment response, but not so long as to be futile and increase the risk of side effects.[85] Conventionally, treatments in AA are continued for at least 6 months, but stopped if there is an insufficient response.[65,79] Ultimately, the aim of treatment is complete terminal hair regrowth on the scalp and any other body site affected. However, achieving "cosmetically acceptable" regrowth, where the person with AA has hair growth at body sites important to them or can camouflage the hair loss, is a reasonable and pragmatic alternative goal. As it is recognized that SALT scores do not always correlate with patients' distress, the level of regrowth achieved that is regarded as meaningful will vary between individuals.[86,87]

Following the approval by both NICE and Scottish Medicines Consortium (SMC), one JAK inhibitor (ritlecitinib) can be prescribed within the NHS for the management of severe AA in adults and adolescents aged 12 years and older. Although the results of clinical trials have suggested an acceptable drug safety profile, drug safety updates have been issued by the Medicines and Healthcare products Regulatory Agency (MHRA),[17] a 'Black Box' warning by the Food and Drug Administration (FDA),[18] and a safety recommendation by the European Medicines Agency (EMA)[19] regarding

increased risk of venous thromboembolism (VTE), serious cardiovascular events, cancer and death with Janus kinase inhibitors. These drugs should be prescribed with caution in anyone over 65 years old or with risk factors for these conditions. The BAD, in collaboration with the British Hair and Nail Society (BHNS) and Alopecia UK, have jointly issued supplementary guidance regarding the use of ritlecitinib in alopecia areata, which includes anticipated response rates and practical guidance for management.

Whether to start, stop, or change treatment is ultimately a clinical decision based on several factors and made in discussion with the patient. One area of uncertainty is the transition to and between JAK inhibitors, and their use in combination therapy, due to limited real-world experience of using these agents. Current Summary of Product Characteristics (SpC) guidance for ritlecitinib advises against combination with other systemic immunosuppressive medicinal products, suggesting that these agents should be used individually and sequentially.[88] Furthermore, as more systemic agents are approved for treating AA, and for those patients with co-existing immune-mediated inflammatory disorders potentially eligible for other licensed agents, consideration should be given to the most appropriate choice of systemic therapy for that individual.

Despite limited evidence, clinicians frequently recommend topical or oral minoxidil and topical prostaglandin analogues to the eyelashes, as adjunctive therapies in AA, based on their known anagen hair growth-promoting mechanisms of action. They are probably most successful in supporting hair growth once regrowth has started. Reports of improved treatment responses when minoxidil is combined with JAK inhibitors[89] or other systemic agents and potential ability of minoxidil to reduce longer-term relapse rates[90] needs confirmation. As some patients starting minoxidil may experience increased hair shedding in the first few weeks of therapy and upon treatment cessation, they should be counselled specifically about this potential side effect.

Once regrowth has occurred the decision to continue active maintenance therapy, to reduce the risk of relapse, should be considered on a case-by-case basis and reviewed regularly. Tapering the dose may help reduce side effects and allow longer term treatment courses, but this approach needs to be balanced against the risk of relapse. Even when a certain treatment has not resulted in complete regrowth, the improvement in hair coverage may allow transition to alternative, safer and more sustainable localized therapies that previously would not have been suitable for more extensive disease. The need for additional psychological support and/or requirements for a wig should be reviewed regularly.

7.1 Special population

7.1.1 Conception, pregnancy and breastfeeding

It is important to advise all patients of child-bearing potential of the risks and benefits of treatment in the context of pregnancy. This is particularly relevant in AA considering the peak onset and patient

demographics in this disease.[24] A clear risk/benefit discussion is required on a case-by-case basis and additional obstetric advice should be sought, if required. Anecdotally, many women with AA describe improvement in their AA during pregnancy, perhaps relating to the physiological immune changes required to carry a baby to term.

Commonly used AA treatments that can possibly be offered during pregnancy and breastfeeding include topical, intralesional and systemic corticosteroids, topical dithranol and oral ciclosporin. Specific areas to consider are outlined below:

1) ***Systemic corticosteroid***
   Caution is required due to the potential increased risk of cleft palate/lip (based on animal studies, but not proven in humans) and higher risk of preterm delivery. Maternal blood pressure and glucose levels need to be monitored during treatment.
2) ***Ciclosporin***
   It is recommended that pregnant women should undergo close monitoring of their blood pressure, renal function, and glucose levels.

Treatments to avoid in pregnancy include contact immunotherapy, methotrexate, mycophenolate mofetil, JAK inhibitors and minoxidil. Specifically, there are no data on contact immunotherapy in pregnancy or breastfeeding. Therefore, the recommendation is to avoid pregnancy during and up to 6 months post-treatment. Currently, there is insufficient data on the safety profile of JAK inhibitors in pregnancy and these agents should also be avoided during breastfeeding. Topical and oral minoxidil should be avoided during pregnancy, based on animal studies raising concerns regarding placental perfusion. Furthermore, there have been case reports of neonatal hypertrichosis following exposure during pregnancy. Minoxidil has been found to be present in breast milk but is not known to be harmful to the foetus (see Appendix C, Supporting Information which also includes advice on paternal exposure).

7.1.2 Paediatric alopecia areata

Children and young people with AA will have varying degrees of hair loss and may be happy, healthy and not wish to seek treatment. The choice to pursue treatment is not always based on the percentage of hair loss, but additive factors, such as noticeability of the alopecia, peer opinion and the wishes of parents or carers, who may have their own specific expectations, also play a role. Therefore, within this complex dynamic, the wishes of the young person must be balanced with those of their family or carers.

The most appropriate treatment will depend on the age and maturity of the person, the emotional and social impact of their hair loss, their ability to tolerate specific therapies (e.g. intralesional injections) and the potential risk of adverse effects with different treatment options. The relapsing and remitting nature of AA should be carefully explained. Early treatment of alopecia areata may

predict a more favourable outcome,[91] but this must be balanced against medicalisation of the childhood years and potential for developing health anxieties from increased medical intervention and exposure to invasive or painful procedures.

Age-appropriate patient and parent information, including information for schools, can improve the social impact of significant hair loss. The national hair loss charity Alopecia UK provides age-appropriate school and individual resources and can support groups and events for children, as well as provide peer support for individuals and their families. Providing skills and appropriate information to answer peer questions and comments can help and empower the individual to adjust to their change in appearance.

Unfortunately, the evidence base for treatment of AA in the paediatric population is poor, with many treatment strategies extrapolated from data in the adult population. Therefore, it is vital that future clinical trials, disease registers and other clinical studies should include children and young people, wherever possible, to guide treatment, inform patient stratification and provide an evidence base for clinical management options. Generally, when therapies are chosen to treat AA in young people, the least invasive and safer options are usually chosen first. Topical corticosteroid (any age) and contact immunotherapy (5 years +) are generally well tolerated in this population.

Children and young people may choose to wear a wig to cover their hair loss. Children may find their wigs wear out more quickly depending on activities undertaken. The UK charity The Little Princess Trust (https://www.littleprincesses.org.uk) will provide one human hair wig to children and young people with hair loss, aged under 24 years.

7.2 Pharmacovigilance

As new, high-cost therapies become available, it is important that we understand the longer-term safety and effectiveness of these treatments specifically in the AA population. The Global Registry of Alopecia areata disease Severity and Treatment Safety (GRASS)-UK (www.bad.org.uk/research-journals/research/grass-uk/) is a BAD-supported, prospective pharmacovigilance register based at the University of Manchester, and part of an international collaboration (GRASS-International) designed to generate harmonised high-quality, real-world data for existing and emerging AA therapies.[92] All people with moderate-to-severe AA should be encouraged to register for this study, where available.

8.0 RECOMMENDED AUDIT POINTS

In the last 20 consecutive people with AA, is there clear documentation of:

1. Provision of a PIL on the condition (e.g. https://www.skinhealthinfo.org.uk/a-z-conditions-treatments/)?
2. Objective severity assessment of AA [e.g. Severity of Alopecia Tool (SALT), Investigator's Global Assessment (IGA) grading] at first presentation / prior to starting any new therapy?

3. Assessment of psychological/psychosocial and functional impact at first presentation?
4. Quality-of-life assessment (e.g. DLQI) at first presentation?
5. Screening for suicide risk assessment for all people identified as having moderate-to-severe psychological distress at any timepoint?
6. Assessment of nail, eyebrow, eyelash or beard involvement at first presentation?
7. A potent topical/intralesional corticosteroid offered to treat limited-to-moderate disease?
8. Safety advice for patients undergoing contact immunotherapy?
9. Medical photography at first presentation?
10. Provision of information on wigs, if clinically indicated?
11. Assessment of JAK inhibitor risk factors, referenced by the drug safety update issued by MHRA, FDA or EMA, prior to starting treatment?

The audit recommendation of 20 cases per department is to reduce variation in the results due to a single person and allow benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months. See Appendix M (Supporting Information) for the set of audit standards, data items and data collection methodology.

9.0 EXTERNAL REVIEW: STAKEHOLDER INVOLVEMENT AND PEER REVIEW

The draft manuscript and the Supporting Information document were made available to the BAD membership, British Hair and Nail Society (BHNS), the Primary Care Dermatological Society (PCDS), the British Dermatological Nursing Group (BDNG) and Alopecia UK. All comments were actively considered by the GDG, and the guideline was updated where appropriate. Following further review, the finalized version was sent for peer review by the Clinical Standards Unit of the BAD, made up of the Therapy & Guidelines subcommittee, prior to submission for publication.

Upon publication in a peer-reviewed journal, the guideline will also be freely available to access on the BAD website.

10.0 LIMITATIONS OF THE GUIDELINE

This document has been prepared on behalf of the BAD and is based on the best data available at the time of writing. It is recognized that under certain conditions it may be necessary to deviate from the guidelines and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence. Limiting the review to English language references was a pragmatic decision, but the authors recognize this may exclude some important information published in other languages.

11.0 PLANS FOR GUIDELINE REVISION

The proposed literature surveillance will be scheduled at ≤6 months, with a view to publish (in the absence of a trigger) appropriate updates 12 months post-publication of the previous guideline iteration.

All recommendations will be treated as living. The literature surveillance may lead to amendments in some recommendations and/or the addition of new recommendations, requiring issuance of the next iteration of this living guideline. The next iteration of this living guideline will indicate all changes made to the content, including from a methodological/living guideline maintenance perspective, to enable convenient access to the updated information.

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Figure Legend

Figure 1. Management pathway for people with alopecia areata
AA, alopecia areata; AEs, adverse events; CYP, children and young people; PIL, Patient Information Leaflet; SALT, Severity of Alopecia Tool

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's website:
Appendix A: Review Protocol
Appendix B: Forest plots
Appendix C: Linking Evidence To Recommendations (LETR)

- Relative values of different outcomes
- Balance between desirable and undesirable effects
- Certainty of evidence
- Patient values and preferences

- Cost
- Other considerations
- List of recommendations

Appendix D: GRADE evidence tables
Appendix E: Summary of included comparative studies
Appendix F: Summary of included within patient studies
Appendix G: Summary of included non-comparative studies
Appendix H: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram – study selection
Appendix I: Risk of Bias analysis
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Appendix N: SALT score aid
Appendix O: Scoring guidance for mental health patient-reported outcome measures (PROMS)

Strength	Wording	Symbols	Definition
Strong recommendation *for* the use of an intervention	"Offer" *(or similar, e.g. "Use", "Provide", "Take", "Investigate", etc.)*	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention whilst only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policy makers, it would be a useful performance indicator.
Weak recommendation *for* the use of an intervention	"Consider"	↑	Risks and benefits of the intervention are finely balanced; most patients would choose the intervention, but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policy makers it would be a poor performance indicator where variability in practice is expected.
No recommendation		Θ	Insufficient evidence to support any recommendation.
Strong recommendation *against* the use of an intervention	"Do not offer"	↓↓	Risks of the intervention outweigh the benefits; most patients would *not* choose the intervention whilst only a small proportion would; for clinicians, most of their patients would *not* receive the intervention.

Table 1. The strength of recommendation

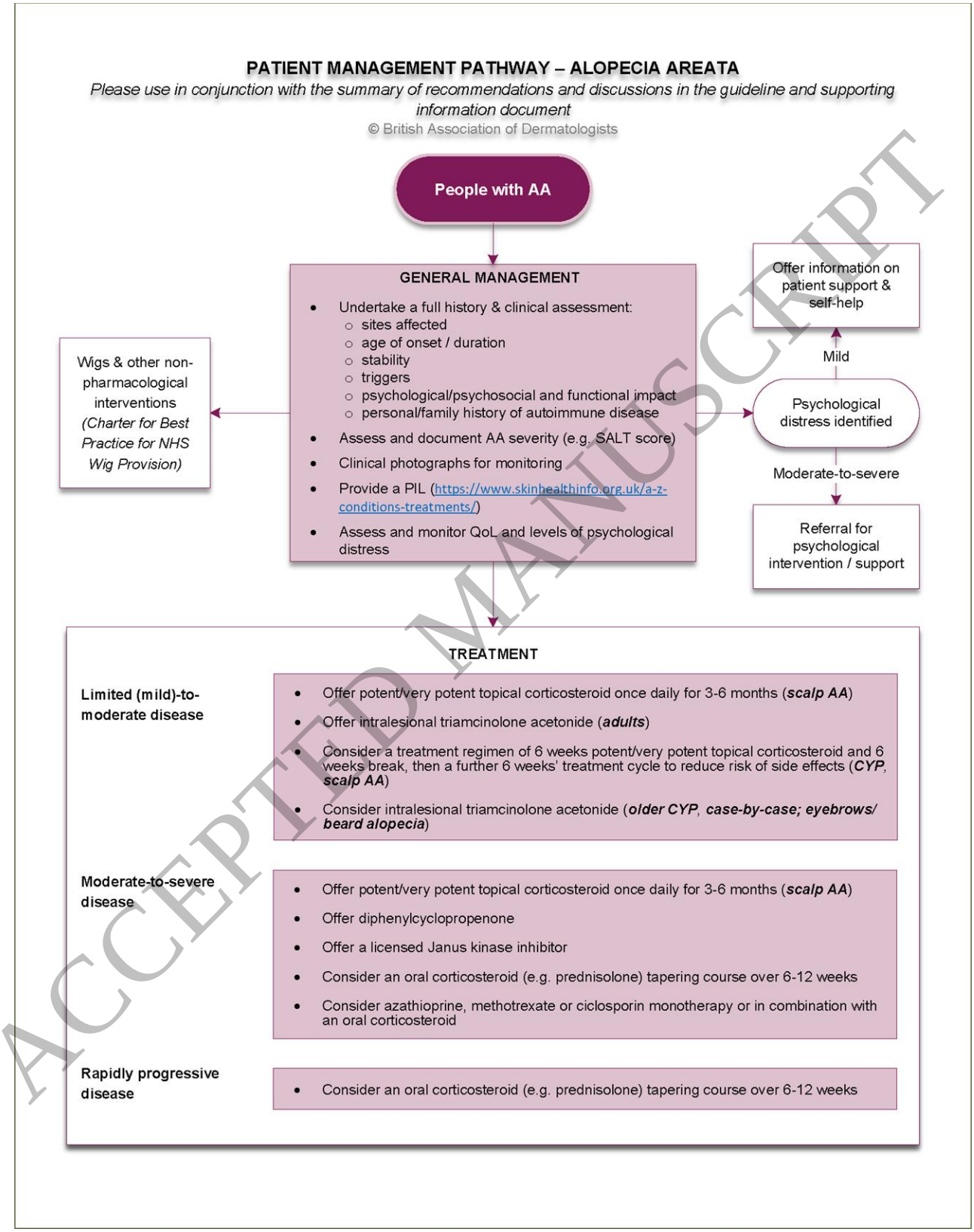

Figure 1
168x215 mm (x DPI)