

## Guidelines

# Guidelines for the management of alopecia areata

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### Summary

These guidelines for management of alopecia areata have been prepared for dermatologists on behalf of the British Association of Dermatologists. They present evidence-based guidance for treatment, with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of epidemiological aspects, diagnosis and investigation.

### Disclaimer

These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data: the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients or special circumstances. Just as adherence to these guidelines may not constitute a defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

### Introduction

Alopecia areata is a chronic inflammatory disease which affects the hair follicles and sometimes the nails. The onset may be at any age and there is no known race or sex preponderance. Alopecia areata usually presents as patches of hair loss on the scalp but any

hair-bearing skin can be involved. The affected skin may be slightly reddened but otherwise appears normal. Short broken hairs (exclamation mark hairs) are frequently seen around the margins of expanding patches of alopecia areata. The nails are involved in about 10% of patients referred for specialist advice. Data from secondary and tertiary referral centres indicate that 34–50% of patients will recover within 1 year, although almost all will experience more than one episode of the disease, and 14–25% progress to total loss of scalp hair (alopecia totalis, AT) or loss of the entire scalp and body hair (alopecia universalis, AU), from which full recovery is unusual (< 10%).<sup>1,2</sup> One study from Japan reported that spontaneous remission within 1 year occurred in 80% of patients with a small number of circumscribed patches of hair loss.<sup>3</sup> The prognosis is less favourable when onset occurs during childhood<sup>1,4–6</sup> and in ophiasis<sup>6</sup> (alopecia areata of the scalp margin). The concurrence of atopic disease has been reported to be associated with a poor prognosis<sup>3,6</sup> but this has been disputed.<sup>7</sup>

About 20% of people with alopecia areata have a family history of the disease, indicating a genetic predisposition.<sup>8</sup> Associations have been reported with a variety of genes, including major histocompatibility complex, cytokine and immunoglobulin genes, suggesting that the genetic predisposition is multifactorial in nature. The hair follicle lesion is probably mediated by T lymphocytes.<sup>9</sup> The association between alopecia areata and other autoimmune diseases suggests that

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alopecia areata is itself an autoimmune disease, although this is unproven.

## Diagnosis

The diagnosis of alopecia areata is usually straightforward although the following may cause diagnostic difficulties:

- Trichotillomania: this condition probably causes most confusion and it is possible that it coexists with alopecia areata in some cases. The incomplete nature of the hair loss in trichotillomania and the fact that the broken hairs are firmly anchored in the scalp (i.e. they remain in the growing phase, anagen, unlike exclamation mark hairs) are distinguishing features
- Tinea capitis: the scalp is inflamed in tinea capitis and there is often scaling but the signs may be subtle
- Early scarring alopecia
- Telogen effluvium
- Anagen effluvium (drug-induced) may mimic diffuse alopecia areata
- Systemic lupus erythematosus
- Secondary syphilis

Occasionally, alopecia areata presents as diffuse hair loss which can be difficult to diagnose. The clinical course often reveals the true diagnosis but a biopsy may be necessary in some cases.

## Investigations

Investigations are unnecessary in most cases of alopecia areata. When the diagnosis is in doubt appropriate tests may include:

- Fungal culture
- Skin biopsy
- Serology for lupus erythematosus
- Serology for syphilis

The increased frequency of autoimmune disease in patients with alopecia areata is probably insufficient to justify routine screening.

## Management

An overriding consideration in the management of alopecia areata is that, although the disease may have a serious psychological effect, it has no direct impact on general health that justifies the use of hazardous treatments, particularly of unproven efficacy. In addition, many patients, although by no means all, experience spontaneous regrowth of hair.

## Counselling

An explanation of alopecia areata, including discussion of the nature and course of the disease and the available treatments, is essential. Some patients are profoundly upset by their alopecia and may require psychological support. Contact with other sufferers and patient support groups may help patients adjust to their disability. The decision to treat alopecia areata actively should not be taken lightly. Treatment can be uncomfortable for the patient, time consuming and potentially toxic. It may also alter the patient's attitude to their hair loss. Some patients find it difficult to cope with relapse following or during initially successful treatment and they should be forewarned of this possibility. These considerations are particularly important in children where the social disruption and focusing of the child's attention on their hair loss, which may result from active treatment, have to be weighed carefully against the potential benefits. On the other hand, some patients are appreciative that something has been tried, even if it does not work.

## Treatment

A number of treatments can induce hair growth in alopecia areata but none has been shown to alter the course of the disease. The high rate of spontaneous remission makes it difficult to assess efficacy, particularly in mild forms of the disease. Some trials have been limited to patients with severe alopecia areata where spontaneous remission is unlikely. However, these patients tend to be resistant to all forms of treatment and the failure of a treatment in this setting does not exclude efficacy in mild alopecia areata. Few treatments have been subjected to randomized controlled trials and, except for contact immunotherapy, there are few published data on long-term outcomes.

### *No treatment*

Leaving alopecia areata untreated is a legitimate option for many patients. Spontaneous remission occurs in up to 80% of patients with limited patchy hair loss of short duration (< 1 year),<sup>3</sup> although the remission rate in patients reaching secondary care is lower. Many patients may therefore be managed by reassurance alone, with advice that regrowth cannot be expected within 3 months of the development of any individual patch.

The prognosis in long-standing extensive alopecia is poor. However, all treatments have a high failure rate in this group and some patients prefer not to be treated, other than wearing a wig if appropriate.

### *Corticosteroids*

*Topical corticosteroids (Strength of recommendation C, Quality of evidence III; see Appendix 1).* Potent topical corticosteroids are widely used to treat alopecia areata but there is little evidence that they promote hair regrowth. A randomized controlled trial of 0.25% desoximetasone cream in 70 patients with patchy alopecia areata failed to show a significant effect over placebo.<sup>10</sup> Topical corticosteroids are ineffective in AT/AU.<sup>11,12</sup> Folliculitis is a common side-effect of topical corticosteroid treatment.

*Intralesional corticosteroids (Strength of recommendation B, Quality of evidence III).* Depot corticosteroid injected intralesionally stimulates hair regrowth at the site of injection in some patients. Porter and Burton reported that tufts of hair grew in 33 of 34 sites injected with triamcinolone hexacetonide in 11 patients with alopecia areata and in 16 of 25 sites injected with triamcinolone acetonide in 17 patients. The effect lasted about 9 months.<sup>13</sup> In a study from Saudi Arabia 62% of patients achieved full regrowth with monthly injections of triamcinolone acetonide, the response being better in those with fewer than five patches of < 3 cm in diameter.<sup>14</sup> This method is most suitable for treating patchy hair loss of limited extent and for cosmetically sensitive sites such as the eyebrows. Hydrocortisone acetate (25 mg mL<sup>-1</sup>) and triamcinolone acetonide (5–10 mg mL<sup>-1</sup>) are commonly used. Corticosteroid is injected just beneath the dermis in the upper subcutis. A 0.05–0.1 mL injection will produce a tuft of hair growth about 0.5 cm in diameter. Multiple injections may be given, the main limitation being patient discomfort. Intralesional corticosteroids may also be administered by a needleless device (e.g. Dermajet™). The device should be sterilized between patients. Abell and Munro reported that 52 of 84 patients (62%) showed regrowth of hair at 12 weeks after three injections of triamcinolone acetonide using the Porto Jet needleless device compared with one of 15 (7%) control subjects injected with isotonic saline.<sup>15</sup> The results were less favourable in AT than in localized alopecia. Skin atrophy at the site of injection is a consistent side-effect of intralesional corticosteroid therapy, particularly if triamcinolone is used, but this

usually resolves after a few months. Repeated injection at the same site or the use of higher concentrations of triamcinolone should be avoided as this may cause prolonged skin atrophy. There is a risk of cataract and raised intraocular pressure if intralesional corticosteroids are used close to the eye, e.g. for treating eyebrows.<sup>16</sup> There is a single case report of anaphylaxis in a patient receiving intralesional triamcinolone acetonide for treatment of alopecia areata.<sup>17</sup> Intralesional corticosteroids are not appropriate in rapidly progressive alopecia nor in extensive disease.

*Systemic corticosteroids (Strength of recommendation C, Quality of evidence III).* Long-term daily treatment with oral corticosteroids will produce regrowth of hair in some patients. One small partly controlled study reported that 30–47% of patients treated with a 6-week tapering course of oral prednisolone (starting at 40 mg daily) showed > 25% hair regrowth.<sup>18</sup> Unfortunately, in most patients continued treatment is needed to maintain hair growth and the response is usually insufficient to justify the risks.<sup>19</sup> There are several reports of high-dose pulsed corticosteroid treatment employing different oral and intravenous regimens (intravenous prednisolone 2 g,<sup>20</sup> intravenous methylprednisolone 250 mg twice daily for 3 days,<sup>21,22</sup> oral prednisolone 300 mg once monthly,<sup>23</sup> dexamethasone 5 mg twice weekly<sup>24</sup>). The differences in treatment protocols and patient selection make it difficult to compare these studies directly, and none was controlled. Overall, about 60% of patients with extensive patchy alopecia showed a cosmetically worthwhile response to pulsed corticosteroids, whereas fewer than 10% of those with ophiasiform disease and AT/AU responded. The oral and intravenous routes of administration appear equally effective. Significant side-effects have not yet been reported with pulsed administration of systemic corticosteroids in alopecia areata. However, short- and long-term hazards of systemic corticosteroids are well known and potentially severe, and in view of these dangers it is not possible to support their use until there is better evidence of efficacy.

### *Contact immunotherapy (Strength of recommendation B, Quality of evidence II-ii)*

Contact immunotherapy was introduced by Rosenberg and Drake in 1976.<sup>25</sup> The contact allergens that have been used in the treatment of alopecia areata include 1-chloro-2,4-dinitrobenzene (DNCEB), squaric acid dibutylester (SADBE) and 2,3-diphenylcyclopropenone

(DPCP). DNCB is mutagenic against *Salmonella typhimurium* in the Ames test<sup>26</sup> and is no longer used. Neither SADBE nor DPCP are mutagenic. One DPCP precursor is mutagenic<sup>27</sup> and batches should be screened for contaminants by the supplier. DPCP is more stable in solution and is usually the agent of choice.

The protocol for contact immunotherapy using DPCP was described by Happle *et al.*<sup>28</sup> The patient is sensitized using a 2% solution of DPCP applied to a small area of the scalp. Two weeks later the scalp is painted with a weak solution of DPCP, starting at 0.001%, and this is repeated at weekly intervals. The concentration is increased at each treatment until a mild dermatitis reaction is obtained. Some clinicians treat one side of the scalp initially to distinguish between a treatment response and spontaneous recovery if hair regrowth occurs. Once hair regrowth is observed, both sides of the scalp are treated. In patients with severe long-standing alopecia, in whom spontaneous recovery is unusual, this precaution is unnecessary. Opinions are divided on whether patients should be allowed to treat themselves.

Once a maximum response is achieved most practitioners reduce the frequency of treatment. In patients in whom full regrowth of hair is obtained treatment can be discontinued. Subsequent relapses will usually respond to further contact immunotherapy, although this cannot be guaranteed.

A review of all the published studies of contact immunotherapy concluded that 50–60% of patients achieve a worthwhile response but that the range of response rates was very wide (9–87%).<sup>29</sup> Patients with extensive hair loss are less likely to respond.<sup>30,31</sup> Other reported adverse prognostic features include the presence of nail changes, early onset and a positive family history.<sup>29</sup> In most studies treatment has been discontinued after 6 months if no response is obtained. In a large case series from Canada clinically significant regrowth occurred in about 30% of patients after 6 months of treatment but this increased to 78% after 32 months of treatment, suggesting that more prolonged treatment is worthwhile.<sup>32</sup> The response in patients with AT/AU was less favourable at 17% and this was not improved by treatment beyond 9 months. Relapses may occur following or during treatment. In the Canadian series relapse following successful treatment occurred in 62% of patients.

Two case report series of contact immunotherapy in children with alopecia areata reported response rates of 33%<sup>33</sup> and 32%.<sup>34</sup> A third study found a similar short-

term response in children with severe alopecia areata, but < 10% experienced sustained benefit.<sup>35</sup>

*Adverse effects.* Most patients will develop occipital and/or cervical lymphadenopathy during contact immunotherapy. This is usually temporary but may persist throughout the treatment period. Severe dermatitis is the most common adverse event but the risk can be minimized by careful titration of the concentration. Uncommon adverse effects include urticaria,<sup>36</sup> which may be severe,<sup>37</sup> and vitiligo.<sup>38,39</sup> Cosmetically disabling pigmentary complications, both hyper- and hypopigmentation (including vitiligo), may occur if contact immunotherapy is used in patients with racially pigmented skin. Such patients should be warned of this risk before embarking on treatment. Contact immunotherapy has been in use for 20 years and no long-term side-effects have been reported.

*Precautions.* Contact immunotherapy is an unlicensed treatment that uses a nonpharmaceutical grade agent. Patients should be fully informed about the nature of the treatment; they should be given an information sheet and give signed consent. Great care must be taken to avoid contact with the allergen by handlers, including pharmacy, medical and nursing staff, and other members of the patient's family. Those applying the allergen should wear gloves and aprons. There are no data on the safety of contact immunotherapy during pregnancy and it should not be used in pregnant women nor in women intending to become pregnant. Owing to these concerns about sensitization and the extent of the measures required to prevent this, and also because of the possible risks in pregnancy, availability of contact immunotherapy is limited and many departments are unwilling to provide this treatment.

DPCP is degraded by light. Solutions should be stored in the dark and patients should wear a hat or wig for 24 h following application.

#### *Phototherapy and photochemotherapy*

*Ultraviolet B treatment.* Although ultraviolet (UV) B erythema has been used in much the same way as other skin irritants there is little documented evidence of efficacy.

*Psoralen plus ultraviolet A treatment (Strength of recommendation C, Quality of evidence III).* There are several uncontrolled studies of psoralen plus UVA (PUVA) treatment for alopecia areata, using all types of PUVA

(oral or topical psoralen, local or whole body UVA irradiation),<sup>40–43</sup> claiming success rates of up to 60–65%. Two retrospective reviews have reported low response rates<sup>44</sup> or suggested that the response was no better than the natural course of the disease,<sup>45</sup> although these observations were also uncontrolled. The relapse rate following treatment is high and continued treatment is usually needed to maintain hair growth, which may lead to an unacceptably high cumulative UVA dose.

*Minoxidil (Strength of recommendation C, Quality of evidence IV)*

An early double-blind study reported a significantly greater frequency of hair regrowth in patchy alopecia areata in patients treated with topical 1% minoxidil compared with placebo.<sup>46</sup> Subsequent controlled trials in patients with extensive alopecia areata using 1% or 3% minoxidil failed to confirm these results.<sup>47–49</sup> Two of these studies reported a treatment response during an extended but uncontrolled part of the trial.<sup>48,49</sup> In one study comparing 5% and 1% minoxidil in extensive alopecia areata regrowth of hair occurred more frequently in those receiving 5% minoxidil but few subjects obtained a cosmetically worthwhile result.<sup>50</sup> Topical minoxidil is ineffective in AT and AU.

*Dithranol (Strength of recommendation C, Quality of evidence IV)*

There is a small number of case report series of dithranol (anthralin) or other irritants in the treatment of alopecia areata.<sup>51–53</sup> The lack of controls makes the response rates difficult to evaluate but only a small proportion of patients seems to achieve cosmetically worthwhile results. In one open study 18% of patients with extensive alopecia areata achieved cosmetically worthwhile hair regrowth.<sup>51</sup> The published data indicate that dithranol needs to be applied sufficiently frequently and in a high enough concentration to produce a brisk irritant reaction in order to be effective. Staining of hair limits its use in fair-haired individuals.

*Miscellaneous*

The dual properties of ciclosporin as an immunosuppressive drug and as a hypertrichotic agent make it a logical choice in treating alopecia areata and this is supported by animal studies. Although there is only a

small number of published uncontrolled trials with low patient numbers the evidence that ciclosporin does stimulate hair regrowth in some patients with alopecia areata is convincing.<sup>54</sup> However, as ciclosporin has to be given orally (it is not active topically) side-effects are a major consideration and, in patients with severe alopecia areata, the cosmetically worthwhile response rate is probably too low to justify the risks<sup>55</sup> (*Strength of recommendation D, Quality of evidence III*).

Treatments which were ineffective in controlled trials include oral zinc<sup>56</sup> and isoprinosine.<sup>57</sup> One randomized double-blind trial showed a significant positive effect of aromatherapy.<sup>58</sup> This awaits confirmation.

*Wigs*

For many female patients with extensive alopecia areata a wig or hairpiece is the most effective solution.<sup>59</sup> Some men also request a wig although male wigs rarely appear as natural. Acrylic wigs are much cheaper than real hair wigs and are easier to look after. However, some patients prefer bespoke real hair wigs, mainly because the better fit allows a wider range of social activities. National Health Service (NHS) charges for wigs are laid out in NHS leaflet HC12 (currently £50.70 for an acrylic wig and £195.40 for a bespoke human hair wig). Information on entitlement to free wigs is given in leaflet HC11.

## Summary of recommendations

Alopecia areata is difficult to treat and few treatments have been assessed in randomized controlled trials. The tendency to spontaneous remission and the lack of adverse effects on general health are important considerations in management, and not treating is the best option in many cases. On the other hand, alopecia areata may cause considerable psychological and social disability and in some cases, particularly those seen in secondary care, it may be a chronic and persistent disease causing extensive or universal hair loss. In those cases where treatment is appropriate there is reasonable evidence to support the following:

- *Limited patchy hair loss*: Intralesional corticosteroid (B III).

Intralesional corticosteroids stimulate hair regrowth at the site of injection. The effect is temporary, lasting a few months, and it is unknown whether the long-term outcome is influenced.

- *Extensive patchy hair loss*: Contact immunotherapy (B II-ii)

- *Alopecia totalis/universalis*: Contact immunotherapy (B II-ii).

Contact immunotherapy is the best-documented treatment in severe alopecia areata but it is not widely available, involves multiple visits to hospital over several months and stimulates cosmetically worthwhile hair regrowth in < 50% of patients with extensive patchy hair loss. It is the only treatment likely to be effective in AT/AU although the response rate in such patients is even lower. It may cause troublesome temporary local inflammation but serious side-effects are rare.

Potent topical corticosteroids and, to a lesser extent, dithranol and minoxidil lotion, are widely prescribed by dermatologists for limited patchy alopecia areata, and are safe, but there is no convincing evidence that they are effective.

Continuous or pulsed systemic corticosteroids and PUVA have also been used to treat alopecia areata. However, in view of the potentially serious side-effects and inadequate evidence of efficacy, none can be recommended at this time.

Children may be treated in a similar fashion to adults. However, intralesional corticosteroids are often poorly tolerated and many clinicians are reluctant to use aggressive treatments such as contact immunotherapy in children.

### Patient support

National Alopecia Areata Foundation, PO Box 150760, San Rafael, CA 94915-0760, U.S.A. (This organization supports research and publishes several useful patient information sheets and a regular newsletter.)

Hairline International, Lyons Court, 1668 High Street, Knowle, West Midlands B93 OLY, U.K.

### Internet resources

<http://www alopeciaareata.com> (National Alopecia Areata Foundation website.)

<http://www.ehrs.org> (Website of the European Hair Research Society. Links to several alopecia areata sites.)

### Conflict of interests

None of the authors has a financial or commercial interest in any of the treatments discussed. A.G.M. occasionally acts as a consultant to pharmaceutical

companies who manufacture and market products for the treatment of hair loss disorders.

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## Appendix 1

### Strength of recommendations

- A There is good evidence to support the use of the procedure
- B There is fair evidence to support the use of the procedure
- C There is poor evidence to support the use of the procedure
- D There is fair evidence to support the rejection of the use of the procedure
- E There is good evidence to support the rejection of the use of the procedure

### Quality of evidence

- I Evidence obtained from at least one properly designed, randomized controlled trial

- II-i Evidence obtained from well-designed controlled trials without randomization
- II-ii Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one centre or research group
- II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
- III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees
- IV Evidence inadequate due to problems of methodology (e.g. sample size, or length of comprehensiveness of follow-up or conflicts of evidence).