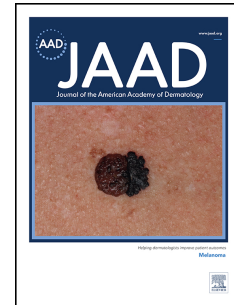


# Journal Pre-proof



The Alopecia Areata Consensus of Experts (ACE) Study PART II: Results of an International Expert Opinion on Diagnosis and Laboratory Evaluation for Alopecia Areata

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**ABSTRACT**

**Background:** We previously reported The Alopecia Areata Consensus of Experts (ACE) Study: Results of an International Expert Opinion on Treatments for Alopecia Areata (AA).

**Objective:** To report the results of the ACE international expert opinion on diagnosis and laboratory evaluation for AA.

**Methods:** Fifty hair experts from 5 continents were invited to participate in a 3 round Delphi process. Consensus threshold was set at  $\geq 66\%$ .

**Results:** Of 148 questions, expert consensus was achieved in 82 (55%) questions. Following round 1 consensus was achieved in 10 of 148 (7%) questions. Round 2 achieved consensus in 47 of 77 questions (61%). The final face-to-face achieved consensus in 25 of 32 (78%) questions. Consensus was greatest for laboratory evaluation (12 of 14 (86%) questions), followed by diagnosis (11 of 14 (79%) questions) of AA. Overall, etiopathogenesis achieved the least category consensus (31 of 68 (46%) questions).

**Limitations:** The study had low representation from Africa, South America and Asia.

**Conclusion:** There is expert consensus on aspects of epidemiology, etiopathogenesis, clinical features, diagnosis, laboratory evaluation and prognostic indicators of AA. The study also highlights areas where future clinical research could be directed to address unresolved hypotheses in AA patient care.

**CAPSULE SUMMARY**

1. This is the first large scale international consensus on the diagnosis and laboratory evaluation of AA.
2. The consensus document identifies potential areas where research may be directed.

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## INTRODUCTION

We previously reported the first part of The Alopecia Areata Consensus of Experts (ACE) Study.<sup>1</sup> In ACE Part II we present international expert consensus on the pathogenesis, diagnosis and laboratory evaluation of alopecia areata (AA).

Treatment is influenced by a greater understanding of the pathogenesis of AA. ACE Part II bridges theory to clinical practice. It considers the frequently posed questions by AA patients and indeed the general dermatologist. It aims to address the nuances often encountered in practice and be clinically relevant for the treating clinician.

There remain many aspects of AA where the available data is inconclusive. Consensus is defined by a general agreement among members of our expert panel, each of whom has exercised discretion in their decision-making. For questions where the threshold for consensus is achieved, few or none achieve unanimous agreement of the experts and until conclusive data emerges, there will remain divergence of opinion. However, when taken together with current AA guidelines,<sup>2-5</sup> ACE Part II provides additional insight into the current opinion from hair experts recognized in the field of AA.

## **METHODS**

### **Expert Panel Selection**

Fifty dermatologists with recognized expertise in hair and scalp disorders were invited to participate.

Wide international representation was reflected in involvement from all five continents.

### **Delphi survey**

The primary questionnaire was designed by a panel of four dermatologists. A systematic literature review was conducted to formulate questions to cover: epidemiology, etiopathogenesis, diagnosis, laboratory evaluation, treatment and prognosis of AA. Importantly, questions specifically included topics of clinical relevance; patient directed questions (e.g. those encountered in patient consultations); and some esoteric concepts.

The Delphi questionnaire was distributed using an online e-management survey system, Delphi Manager, maintained by the COMET (Core Outcome Measures for Effectiveness Trials) Initiative.<sup>6</sup>

### **Delphi process**

The Delphi process has been validated in numerous studies to determine core outcomes<sup>7</sup> and define diagnostic criteria.<sup>8,9</sup> It was selected for ACE as it aims to achieve convergence of opinion through a series of rounds. Submitted answers are anonymized to minimise bias, whilst sequential iterations enable revision of judgement based on peer review to achieve consensus, where possible.<sup>10-13</sup>

ACE involved two questionnaire rounds followed by a final face-to-face meeting (Figure 1). For each questionnaire round, participants were instructed to assign a score for each question from 1-9 or "unable to score". A score of 1 corresponded to strong disagreement and 9 indicated strong agreement.

**Consensus threshold**

Threshold values have varied across Delphi studies.<sup>7,8,14,15</sup> Consensus threshold for ACE was set at  $\geq 66\%$  agreement (scores 7-9) or disagreement (scores 1-3) of the participants scoring a given question or statement at round 1, round 2 or the face-to-face meeting but did not necessarily represent consensus of all 50 participants.

Questions with scores 4-6 were regarded as indeterminate. Questions excluded from the next round included those which had achieved consensus ( $\geq 66\%$ ) and those with a lack of consensus ( $\leq 33\%$ ), given the low probability that these would achieve consensus.

Questions included in the next round included those with consensus values between 33% and 66%.

**Statistical analysis**

R version 3.5.3 statistical software package was used for data analysis.<sup>16</sup>



## RESULTS

### Expert Panel

Of 50 invited hair experts, 41 (82%) completed round 1, 39 (78%) round 2 and 30 (60%) attended the face-to-face meeting at the 11th World Congress for Hair Research (WCHR) in Sitges, Spain. Thirty-six (88%) experts, routinely managed adults and children with hair loss disorders. Twenty-three (56%) work in public (academic institutions) and private practice, 13 (32%) exclusively in private, and 5 (12%) exclusively in public practice. Participants were from Europe (15; 37%); Asia (3; 7%), Australia (9; 22%) and North America (14; 34%).

### Delphi rounds

Figure 2 summarizes the ACE Delphi rounds. 148 questions related to epidemiology, etiopathogenesis, clinical features, diagnosis, laboratory evaluation, prognosis and prognostic indicators. Expert consensus was achieved in 82 questions (55%), including 10, 47 and 25 questions following rounds 1, 2 and 3 respectively. The category with the greatest consensus was laboratory evaluation (12 of 14 (86%) questions), followed by diagnosis (11 of 14 (79%) questions). The least consensus achieved was for etiopathogenesis (31 of 68 (46%) questions).

## CONSENSUS OUTCOME

### 1.0 Epidemiology

Six questions related to epidemiology. Consensus was achieved in 3 questions (50%).

- Ethnicity (race) does not alter the natural history/prognosis of AA.
- Neither ethnicity nor climate/geographical latitude influences the risk of a poor response to treatment.

## 2.0 Etiopathogenesis

Sixty-eight questions related to etiopathogenesis, subdivided into; family history, genetics, autoimmune disease, allergic comorbidities, associated comorbidities, nutritional, stress, and environmental. Consensus was achieved in 31 questions (46%).

- Factors that were considered to increase the risk of developing AA include: a family history of AA/organ specific autoimmune disease; genotype; a personal history of autoimmune disease/thyroid disease/vitiligo/atopy or atopic dermatitis. Iron deficiency and pregnancy were not considered to increase the risk of developing AA.
- Factors that were considered to influence the natural history/prognosis of AA include genotype; a personal history of autoimmune disease or atopy. Iron deficiency and vaccination were not considered to influence the natural history/prognosis of AA.
- Factors that were considered to trigger initial disease and episodic relapse(s) include genotype with environmental trigger; major traumatic life event; acute stress.
- Factors that were considered to influence the response to treatment include genotype. Iron deficiency and vaccination were not considered to influence the response to treatment.

## 3.0 Clinical Features

Consensus was achieved in 11 (48%) of 23 questions regarding clinical features:

- Signs indicating disease activity include: exclamation mark hairs; trichoscopic black dots; a positive hair pull test; anagen effluvium.
- Severity of Alopecia Tool Score (SALT) + Quality of life (QoL) (e.g. Dermatology Life Quality Index (DLQI)) or SALT + Scalp Surface Area (SSA) + QoL are required in clinical trials involving adults or children.
- SALT is a sufficient measure of disease extent in clinical practice in adults and children.

#### 4.0 Diagnosis

Consensus was achieved in 11 (79%) of 14 questions relating to the diagnosis of AA:

- AA diagnosis can be determined by clinical examination and trichoscopic findings.
- Hair pluck trichograms are not useful in the diagnosis of AA.
- Scalp biopsy is indicated in the following circumstances: a solitary patch recalcitrant to treatment; diffuse alopecia; and when cicatricial alopecia cannot be excluded clinically.
- When performing scalp biopsies in AA, it is usually sufficient to take one single biopsy (for horizontal and vertical sectioning) to confirm the diagnosis of AA, but occasionally two or more biopsies (for horizontal and vertical sectioning) may be needed.
- Biopsy site should be from the edge of a lesion (not the center), and preferably from a lesion located at a site normally resistant to androgenetic alopecia (e.g. occipital scalp).
- An additional scalp biopsy from non-lesional scalp is not considered important.

#### 5.0 laboratory evaluation

Consensus was achieved in 12 (86%) of 14 statements regarding laboratory evaluation of AA:

- Fungal microscopy should not be performed routinely and is only required when there is clinical suspicion of tinea capitis.
- Routine blood tests (full blood count, renal and liver function) and screening for autoimmune disease, connective tissue disease, celiac disease, pernicious anemia and diabetes are not required and should not be performed in all patients at the time of diagnosis of AA.
- In the absence of relevant clinical symptoms and signs, viral serology is not useful to identify a potential AA episode trigger.

- Early morning cortisol is not a useful test in patients who believe stress may have triggered an AA episode.
- Prior to initiation of systemic treatment of AA, investigation is identical to requirements for other dermatological diseases.

## 6.0 Prognosis and Prognostic indicators

The effect of disease duration and disease phenotype on AA progression was addressed. Poor prognosis in this context referred to developing a severe disease phenotype but did not imply refractory to treatment; and response to treatment was queried separately. Consensus was achieved in 14 (61%) of 23 questions.

- Prognosis is worse when AA persists beyond 5 years.
- Hair loss can become irreversible when AA persists for 10 years but should not be assumed to be so or contraindicate a trial of therapy.
- Development of lesions of alopecia can be influenced by systemic factors e.g. metabolic (hormones) and immunological (proinflammatory cytokines) factors.
- Ophiasis phenotype indicates poor prognosis.
- Eyebrow, eyelash and non-scalp hair loss indicates poor prognosis.
- Nail pitting suggests an increased risk of developing AT/AU, worsens AA prognosis and reduces response to treatment.
- Trachyonychia suggests an increased risk of developing AT/AU and worsens AA prognosis.

### NON-CONSENSUS OUTCOME

Table 1 summarizes non consensus outcomes. Consensus was not achieved in 66 questions (45%); 61, 0 and 5 questions following rounds 1, 2 and 3, respectively.

## DISCUSSION

ACE Part II represents the largest international expert consensus study on the diagnosis and laboratory evaluation for AA achieved via the Delphi process.

Consensus was achieved for genotype increasing the risk of developing AA, affecting the prognosis of AA and influencing the response to treatment of AA. AA is considered a complex polygenic disorder and the genetic aetiology is well described. A positive family history is reported in 20-40% of cases<sup>17</sup> and twin studies have shown high concordance (42%) among monozygotic twins.<sup>18</sup> The first AA genome-wide association study (GWAS) identified eight regions in the genome associated with AA,<sup>19</sup> increasing to 14 susceptibility loci in later studies.<sup>20</sup>

Acute stress was recognized as a trigger for initial disease and episodic relapse(s) of AA. However, tests to confirm a stress trigger (e.g. early morning cortisol) are not useful. Experimental studies have shown increased expression of hypothalamic–pituitary–adrenal (HPA) hormone receptors e.g. corticotrophin-releasing hormone receptor 2,<sup>21</sup> adrenocorticotropin<sup>22</sup> and estrogen receptor 1 in lesional AA hair follicles.<sup>23</sup> There was no consensus on the role of chronic stress as a disease trigger.

Consensus was achieved on the recording of Severity of Alopecia Tool (SALT) as a measure of disease activity both in clinical practice and clinical trials in children and adults. It was acknowledged that additional assessments (SSA, QoL) are required for the purpose of clinical trials. SALT has been validated in several AA studies for use in clinical trials/routine practice. Additional measures such as Alopecia Density and Extent (ALODEX) score<sup>5</sup> have also been proposed.

There was agreement on the site of scalp biopsy. Of note, statement concerning the number of scalp biopsies - two or more biopsies (for horizontal and vertical sectioning), for the histological diagnosis of AA was discussed again at the face to face meeting following a specific request to revisit this was accepted. It was agreed that horizontal and vertical sectioning is important to confirm the histological diagnosis of AA, and that one single biopsy (sectioned horizontally and vertically) is usually sufficient to confirm the diagnosis of AA but that in some instances more than one biopsy may be needed.

Experts felt that clarity on this was essential as a question specifically on performing one single biopsy (sectioned horizontally and vertically) being sufficient for the diagnosis of AA, was not included in the questionnaire.

Consistent with current recommendations,<sup>5</sup> diffuse AA may also necessitate a biopsy. Additional investigations to exclude AA mimickers, e.g. tinea capitis, is indicated only when there is clinical uncertainty. The expert group agreed that autoimmune screening investigations are not required in all AA patients, however, there was no consensus on testing specifically for vitamin D and thyroid disease. In patients with symptoms suggestive of co-existing auto-immune disease appropriate testing will still be required.

There was consensus agreement on worsening prognosis if AA persists beyond 5 years. Ikeda proposed 12 months<sup>24</sup> and the current expert opinion is perhaps a reflection on treatment progress since Ikeda's historical observations in 1965.

Whilst disease duration of greater than 10 years may lead to irreversible hair loss, recommendations were not to exclude such patients from active treatment where available.

Nail disease, particularly pitting, was recognized as a poor prognostic finding with respect to developing a severe disease phenotype and affecting response to treatment. Trachyonychia may also act as a poor prognostic marker but there was no consensus on whether it affects response to treatment. Treatment success of trachyonychia has been reported.<sup>25</sup>

ACE part II identified 66 non consensus questions. The majority (61) emerged following round 1 of the Delphi process and all with <33% consensus. This indicates wide divergence in opinion for these questions. The significant number of questions from etiopathogenesis and prognosis suggests that there is still much to learn and whilst data emerges and research informs, viewpoints may eventually merge.

There are potential limitations to consider. Firstly, whilst there was wide international participation and involvement of academic and community hair experts, there was low expert representation from Africa (n=1) South America (n=0) and Asia (n=3) and over representation from Europe (n=15) and North America (n=14). Secondly, the involvement of a hair scientist in the initial design of the questionnaire, to provide an additional perspective on AA pathogenesis, may have been beneficial. Thirdly, not all participants answered each question when presented the second or third time and 60%(30) attended the final face meeting in Stiges. Fourthly, as previously reported,<sup>1</sup> time constraints to cast votes at the final face-to-face meeting, and influencer bias, as the meeting was not chaired by an independent, non-voting individual, are further possible limitations.

## CONCLUSION

In summary, ACE Part II has provided insight into areas where current expert opinion is divided and where future research could potentially be directed, e.g. etiopathogenesis of AA. As we learn more about AA, the divergence may narrow, but in doing so we are hopeful that ACE Part II will provide a useful framework for dermatologists, health care providers and scientists alike, so that ultimately the greatest beneficiaries are our AA patients. Moreover, ACE has identified the need for an international AA registry, development of which will enable recording of comparable, robust, real-world data, to better inform on the prognostic significance of AA.

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**FIGURE LEGENDS**

Figure 1: The Delphi process in ACE

Figure 2: Summary of results from all Delphi rounds: ACE II

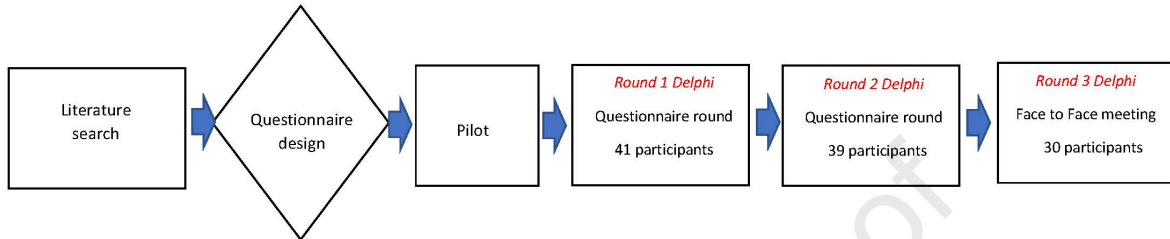
Table 1: Non-consensus outcomes for ACE II

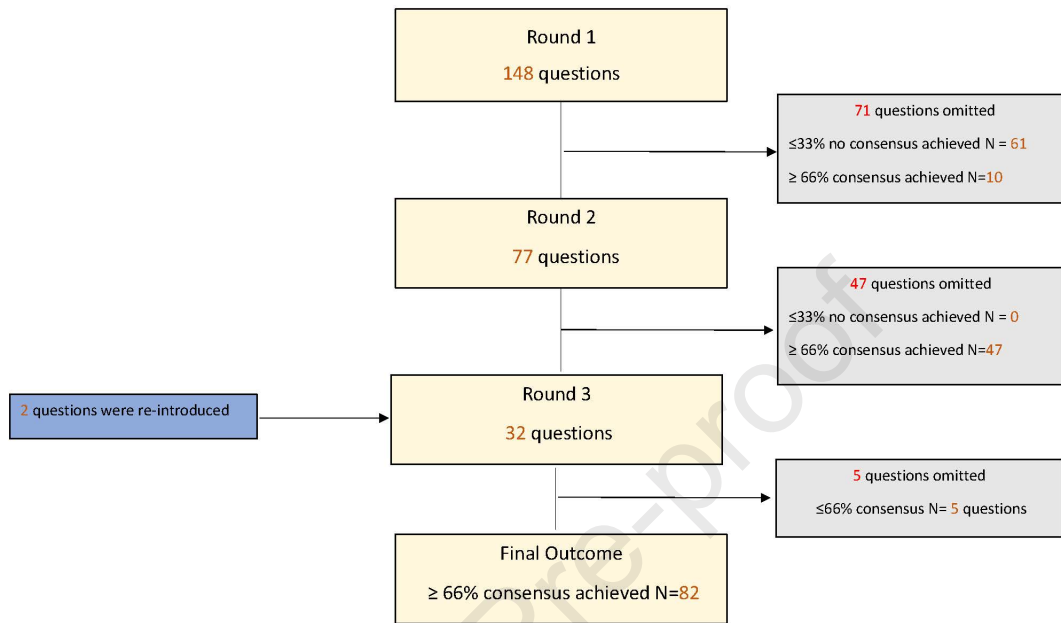
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Table 1: Non-consensus outcomes for ACE II

Category	There was disagreement amongst the experts regarding the following statements
<b>Epidemiology</b>	Ethnicity (race) influences the risk of developing AA. Climate/geographical latitude influences the risk of developing AA and influences the natural history/prognosis of AA.
<b>Etiopathogenesis</b>	<u>Factors that were considered to increase the risk of developing AA include:</u> a family history of atopy; vitamin D deficiency; viral illness and vaccination. <u>Factors that were considered to increase the risk of developing AT/AU include:</u> a family history of organ specific autoimmune disease/atopy; vitamin D deficiency and viral illness <u>Factors that were considered to influence the natural history/prognosis of AA include:</u> a family history of AA/organ specific autoimmune disease/atopy; vitamin D deficiency; pregnancy and viral illness. <u>Factors that were considered to trigger initial disease and episodic relapse(s) include:</u> chronic stress. <u>Factors that were considered to influence response to treatment include:</u> a family history of AA/organ specific autoimmune disease/atopy; a personal history of autoimmune disease/type 1 diabetes /myasthenia gravis /pernicious anaemia/psoriasis /lupus/rheumatoid arthritis/coeliac disease/atopy/asthma/allergic rhinoconjunctivitis/food allergy /allergic contact dermatitis; pregnancy; vitamin D deficiency and viral illness.  Alopecia areata can be seasonal (regardless of geographic location) or cyclical (e.g. same month every year).
<b>Clinical Features</b>	Signs that indicate disease activity (in addition to disease spread) include: telogen effluvium, scalp itch/tingling/dysesthesia and trichoscopic yellow dots.  <u>Outcome measures for clinical trials:</u> <ul style="list-style-type: none"> <li>• SALT is a sufficient measure of disease extent in adults and children</li> <li>• SALT + SSA is required to measure disease severity in children.</li> </ul> <u>Outcome measures for clinical practice:</u> <ul style="list-style-type: none"> <li>• SALT + SSA is required to measure disease severity in adults and children.</li> <li>• SALT + QoL (e.g. DLQI) is required to measure disease severity in adults and children.</li> <li>• SALT + SSA + QoL is required to measure disease severity in adults and children.</li> </ul>
<b>Diagnosis</b>	The optimal method of scalp biopsy is a single scalp biopsy sectioned horizontally or a single biopsy sectioned vertically. Trichograms are useful in the assessment of disease activity in AA.
<b>Laboratory Evaluation</b>	Routine screening bloods should be performed for: vitamin D deficiency and thyroid disease.
<b>Prognosis and prognostic indicators</b>	Active treatment early in the disease affects prognosis. Prognosis is worse when AA persists beyond 6 months/12 months. Hair loss can become irreversible when AA persists for <6 months/12 months/5 years/8years. Development of lesions of alopecia can be influenced by local factors. Trachyonychia alters response to treatment.

Abbreviations: Alopecia Areata (AA); Alopecia areata Consensus of Experts (ACE); Dermatology Life Quality Index (DLQI); Quality of life (QoL); Severity of Alopecia Tool Score (SALT); Scalp Surface Area (SSA).

**Figure 1** The Delphi process in ACE

**Figure 2** Summary of results from all Delphi rounds: ACE II

**CAPSULE SUMMARY**

1. This is the first large scale international consensus on the diagnosis and laboratory evaluation of AA.
2. The consensus document identifies potential areas where research may be directed.

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