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Clinical Management of Atopic Dermatitis in Adults: Mapping of Expert Opinion in 4 Nordic Countries using a Modified Delphi Process

Jacob P. THYSSEN¹, Teresa BERENTS², Maria BRADLEY³, Mette DELEURAN⁴, Øystein GRIMSTAD⁵, Laura KORHONEN⁶, Tor LANGE LAND⁷, Tore SÄRNHULT⁸, Simon Francis THOMSEN⁹, Turid THUNE¹⁰, Carl-Fredrik WAHLGREN³, Christian VESTERGAARD¹¹, Laura B. VON KOBYLETZKI¹² and Anita REMITZ¹³

¹Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark, ²Department of Dermatology and Regional Unit for Asthma, Allergy and Hypersensitivity, Oslo University Hospital-Rikshospitalet, Oslo, Norway, ³Dermatology and Venereology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, ⁴Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark, ⁵Department of Dermatology, University Hospital of North Norway, Tromsø, Norway, ⁶Allergy Centre, Tampere University Hospital, Tampere, Finland, ⁷Langeland Tor, Hudlegene Tor Langeland and Gro Mørk, Oslo, Norway, ⁸Särnhult Tore, Hallandskustens Hudmottagning, Kungsbacka, Sweden, ⁹Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark, ¹⁰Department of Dermatovenereology, Haukeland University Hospital, Bergen, Norway, ¹¹Department of Dermatology and Venereology, Aarhus University Hospital, Aarhus, Denmark, ¹²Department of Dermatology, Lund University, Skåne University Hospital, Malmö, Sweden, and ¹³Department of Skin and Allergic Diseases, Helsinki University Central Hospital, Helsinki, Finland

Similarities and differences in the everyday clinical management of moderate-to-severe atopic dermatitis in Nordic countries are unknown. Using a modified Delphi approach, 15 dermatologists from Denmark, Finland, Norway and Sweden completed face-to-face and online questionnaires and participated in summary discussions to map expert opinion on the clinical management of moderate-to-severe atopic dermatitis in these Nordic countries. Through discussions, 6 adult patient profiles, reflecting common disease presentations of atopic dermatitis, were identified. Using these case profiles, diagnostic work-up, treatment goals, patient education and treatment approaches were discussed. Patient education was identified as essential for effective management. A treatment sequence of moderate-to-potent topical glucocorticosteroids and emollients, followed by systemic treatment, was recommended, allowing 3 months to ascertain systemic treatment response before switching, if necessary. Consensus was not reached on systemic treatment choice, reflecting differences in clinical practice and reimbursement between countries. Practical, case-based clinical recommendations were developed for optimal patient care.

Key words: atopic dermatitis; guidelines; management; Nordic; treatment; work-up.

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Corr: Jacob P. Thyssen, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Kildegaardsvej 28, DK-2900 Hellerup, Denmark. E-mail; jacob.pontoppidan.thyssen@regionh.dk

Atopic dermatitis (AD) is a chronic, pruritic, relapsing skin disease associated with inflammation, skin barrier dysfunction and altered skin microbiota. AD can be associated with elevated serum IgE and cytokine levels, driven by type 2 inflammation, and can occur alongside type I allergy manifestations, such as allergic asthma and rhinitis. The incidence of AD has increased 2–3-fold in the past 3 decades, but appears to have reached

SIGNIFICANCE

Atopic dermatitis is a disease associated with various skin complaints. There is currently no consensus on the diagnosis and treatment of atopic dermatitis in the Nordic region. We therefore gathered 15 Nordic dermatologists to discuss patient education, diagnosis and treatment of atopic dermatitis. Patient education was identified as essential for effective management of atopic dermatitis, and treatment with moderate-to-potent topical glucocorticosteroids and emollients, followed by systemic treatment, was recommended. This article provides insights into the challenges associated with effective management of atopic dermatitis across the Nordic region and provides recommendations for optimal patient care.

a plateau in developed countries (1, 2); AD affects up to 25% of the paediatric population and up to 5% of adults worldwide (2–5), either as a persistent disease from childhood or as recurring or adult-onset AD (6, 7). AD is a heterogeneous disease with a broad spectrum of clinical presentations and differential severity. In addition to these phenotypes, AD also exhibits different endotypes according to different inflammatory mediators, IgE levels and filaggrin gene mutation status, which can vary across different ethnicities and age groups (8, 9). Multiple other factors influence the clinical picture, such as age, sex, environment, occupation and lifestyle. The differential diagnosis is wide-ranging; examples of overlapping or competing conditions that need to be considered include contact dermatitis, skin infections, neurodermatitis, immunodeficiency disorders, drug eruptions and cutaneous T-cell lymphoma (10).

The primary treatment for AD is based on repairing and improving skin barrier function by avoiding exacerbating factors, using emollients and treating active lesions with anti-inflammatory medication (11, 12). Emollients, along with topical anti-inflammatory treatments, including topical glucocorticosteroids (TCS) and topical calcineurin

inhibitors (TCI), are used for managing exacerbations and actively maintaining long-term symptom control (11, 13, 14). Topical treatments can provide symptom control in many patients with AD, but adults with moderate-to-severe AD may require phototherapy or systemic therapy.

Systemic treatments approved for the treatment of moderate-to-severe adult AD include cyclosporine-A, prednisolone (approved for AD in Norway) and the biologic dupilumab (15). Patients with moderate-to-severe AD are also treated using unlicensed systemic therapies, e.g. prednisolone, azathioprine, mycophenolate mofetil and methotrexate (11).

The population affected by AD is heterogeneous, and the factors determining AD management, such as age, comorbidity, pregnancy, course of disease and previous management, extend beyond objective severity. The diverse phenotypes observed in patients with AD should influence how AD is clinically managed (7). Clinical identification of factors that can impact outcomes might provide a means for more effective treatments.

There is limited insight into the similarities and differences in everyday clinical management of moderate-to-severe AD in adults in Nordic countries. Local preferences for AD management differ, which may have a bearing on the treatment selection. Treatment and diagnostic practice vary significantly across and within Nordic countries because both clinical guidance and economic factors are taken into consideration during clinical decision-making. Experts from Denmark, Finland, Norway and Sweden were invited to discuss and come to a possible consensus on the principles of managing AD, considering local differences between countries and sharing experiences.

In this consensus process, 15 dermatologists from Denmark, Finland, Norway and Sweden used a modified Delphi technique to provide patient-focused expert opinion for the work-up and treatment of adults with moderate-to-severe AD for use in a clinical setting. This expert panel, invited by the study sponsor, was independent and was not appointed by a National Dermatological Society or Regulatory Authority from any of the respective countries.

MATERIALS AND METHODS

Development of case profiles

Six patient cases based on common profiles of adult patients with moderate-to-severe AD presenting in Nordic dermatology clinics were identified and described; these cases reflected key patient features of relevance to dermatologists. The Steering Committee used an iterative process, involving 2–3 rounds of drafts and review, to develop case statements ready to vote on during the consensus meeting. For each case, they developed a set of statements and questions on diagnostic work-up and treatment recommendations that were specific to that profile:

1. Presentation, signs and symptoms, patient history and family history

2. Differential diagnosis
3. Work-up: clinical and laboratory investigations from a standard checklist of:
 - Patch and skin prick testing
 - Complete blood count
 - Total and allergen-specific IgE
 - Oral food provocation tests
 - Filaggrin gene mutation testing
 - Tests for *Malassezia furfur* spp. (IgE test, culture and/or microscopy)
 - Identification of bacteria and viruses using cultures and/or PCR
4. Assessment of disease severity (e.g. Eczema Area and Severity Index [EASI] (16), Patient Oriented Eczema Measure [POEM] (17), SCORing Atopic Dermatitis [SCORAD] (18) and impact on HRQoL by means of Dermatology Life Quality Index [DLQI] (19))
5. Goals of treatment
6. Treatment (topical or systemic)
7. Evolution of the case (clinical presentation, patient history and family history)
8. Specific considerations for each case

Modified Delphi process

The Delphi process is a recognized method used to gain consensus between specialists in a particular field where expert opinion is important in shaping judgements. This approach provides experts with an opportunity to alter their response based on their peers' opinions, thus increasing the likelihood of convergence of opinion. The process consisted of questionnaires during the meeting and via online surveys, plus a final validation stage via email.

Expert panel

Recommendations were developed for diagnostic work-up, treatment goals and treatment choice by an expert panel using a modified Delphi process. The expert panel of 15 dermatologists from Denmark, Finland, Norway and Sweden had a particular interest in and knowledge about AD and were selected on the basis of their clinical role and experience of managing patients with AD. The relative geographical contributions from each country were balanced, with 4 advisors each from Denmark, Norway and Sweden and 3 from Finland. Overall, 14 of the experts were involved in the final manuscript validation and the Steering Committee, comprised of one expert from each country, (JT, TB, LVK and AR), developed the 6 hypothetical patient profiles.

Expert consensus panel and follow-up online surveys

During the meeting, the Steering Committee presented each of the 6 patient profiles to the remainder of the expert panel and posed questions as per the modified Delphi method (20); based on advice from the Steering Committee, the questions were case specific. The possible answers were either scored on a 5-point Likert scale or answered using multiple choice responses (for systemic treatment options); in each instance, the experts could select only one answer. During the meeting, responses were captured using audience response voting systems provided by a third party, Crystal Interactive, Godalming, UK (a global meeting and events solution company); this methodology provided anonymous answers and allowed voting to be evaluated by country. Initially, experts voted on whether they agreed that the case profile represented a "typical" AD patient group before moving on to address diagnostic work-up, treatment goals and treatment choice. All responses were reviewed and discussed regardless of the level of consensus. If a consensus

was not reached, experts had a detailed facilitated discussion to identify the reasons for the lack of agreement. Dr Thyssen acted as chair and an independent Delphi facilitator moderated the meeting. Statements were revised by the Delphi facilitator after feedback from experts and re-voting was undertaken when possible. The chair also invited discussion from the experts on what drives their decisions when selecting treatment; this was largely captured in an open discussion.

For each case, statements on diagnostic work-up, patient education, treatment goals and treatment choice were developed, refined and voted on (either in the face-to-face meeting or post-meeting via the online survey).

Owing to time constraints and the extent of discussion required, voting was only completed on all statements for cases 1 and 2, and treatment goals and treatment choice statements were only completed for case 4 during the face-to-face meeting. The priority of the cases discussed in the face-to-face meeting was driven by the expert panel. After the initial meeting, the outcomes (from the aforementioned case studies) were validated, and voting for the statements from the remaining cases (cases 3, 5 and 6 and the diagnostic statements for case 4) was conducted and validated via an online survey. The facilitator shared the results by email and independently collected feedback from each participant. A consensus threshold of 75% was specified *a priori*, which is in keeping with recent consensus initiatives in this field (21).

RESULTS

Case profile validation

The 6 typical patient presentations developed to illustrate the spectra of adult moderate-to-severe AD observed in the clinic are presented in **Table I** and illustrated in **Fig. 1**.

For each case, the advisors reached consensus (100% agreed) that the patient presentation was typical of patients with moderate-to-severe AD commonly managed

in Nordic countries. The advisors also reached consensus (100% agreed) that the cases reflected the spectra of the most typical presentations of adults with moderate-to-severe AD seen in Nordic clinics (Table I). Case 6 prompted the most discussion, given the complex nature and lack of clear definition for late-onset AD (compared with pre-existing AD that has been diagnosed late) and the possibility of alternative diagnoses, such as cutaneous T-cell lymphoma or contact dermatitis.

The importance of accurately detailing patient history was emphasized by the experts, particularly when taking on a new referral (Table I). Patients' EASI scores and family histories were important features, as were relevant comorbidities (Table I). Different features were important for each case; for example, the region of the body affected, the age of the patient, with onset either in infancy or later in life, and details of skin lesions in patients with infected eczema. Incomplete medical notes could lead to erroneous conclusions; for example, patients may overestimate the severity of their allergies when self-reporting, or a perceived treatment failure could have been caused by poor patient compliance or an ineffectively implemented treatment plan. In these cases, previous treatments could potentially be re-attempted.

The results of the final consensus agreements are presented in **Tables II–V** and Figs S1–S6¹.

The discussion and considerations behind these agreements are captured in the discussion section to provide a broader context.

¹<https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-3369>

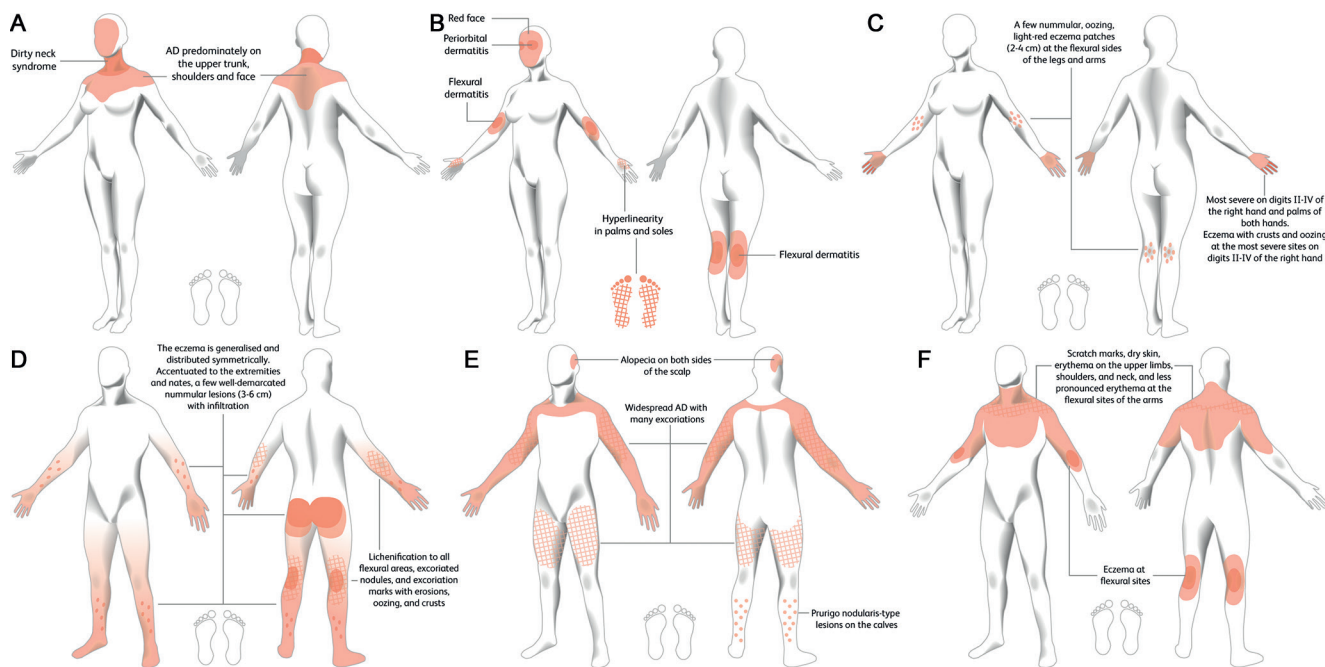


Fig. 1. Clinical characteristics of atopic dermatitis (AD) for 6 typical case presentations. (A) Case 1. Moderate-to-severe head and neck dermatitis. (B) Case 2. Moderate-to-severe AD with type I allergies. (C) Case 3. Moderate-to-severe AD with hand eczema. (D) Case 4. Moderate-to-severe AD with recurrent infections (E) Case 5. Moderate-to-severe lichenified AD with severe itch. (F) Case 6. Moderate-to-severe, late-onset AD.

Table I. Case presentations: details and statements for expert voting

Case 1 Moderate-to-severe head and neck dermatitis	Case 2 Moderate-to-severe AD with type I allergies	Case 3 Moderate-to-severe AD with hand eczema	Case 4 Moderate-to-severe AD with recurrent infections	Case 5 Moderate-to-severe lichenified AD with severe itch	Case 6 Moderate-to-severe, late-onset AD
30-year-old woman with AD and pronounced head and neck dermatitis	24-year-old woman with a history of AD since infancy	20-year-old woman with hand eczema that has been worsening for 14 months; works as a cleaner	35-year-old male computer engineer with AD since infancy; lives alone, no special hobbies, overweight and a smoker	36-year-old man; AD since childhood	70-year-old man with eczema in skin flexures; redness and itching of the back
<i>Presentation</i> Moderate-to-severe eczema with a brownish appearance EASI score: 12	Moderate-to-severe AD EASI score: 18	Suspected occupational exposure to an irritant and/or contact allergen HEES score: 11	Severe itching and sores. Itch and pain are worse at night; 2 days before consultation experienced an exacerbation with severe itch and vesicles, especially on arms, legs and buttocks EASI score: 35 External triggers that exacerbate eczema are cold weather, change in temperature, sweat, water, wool clothing, particular infections and scratching Takes a shower twice a week	Disturbed sleep caused by severe itch that is affecting daily life and impacting personal relationships EASI score: 35.5	Eczema for 3 years and exacerbation for 3 months; sleeplessness and itch for >3 months DLQI score: 15
<i>Clinical characteristics</i> AD predominantly on upper trunk, shoulders and face since early 20s. Patchy dermatitis often pigmented and darker appearance Dirty neck syndrome Has cosmetic concerns and also finds AD itchy and difficult to control. General sleep problems due to itching	Flexural and periorbital dermatitis and "red face". Hyperlinearity on palms and soles	Severe, generalized AD and increasingly severe hand eczema; dry, scaly eczematous skin, especially at the sides of the proximal phalanges of digits II–V of both hands. Most severe on digits II–IV of right hand and palms of both hands. Eczema with crusts and oozing at most severe sites on digits II–IV of the right hand A few nummular, oozing, light-red eczema patches (2–4 cm) at flexural sides of legs and arms	Eczema generalized and distributed symmetrically. Accentuated to extremities and nates; eczema consists of papules, vesicles, deep erythema, erosions, yellow crusts, oozing and a few well-demarcated nummular lesions 3–6 cm in diameter with infiltration Lichenification to all flexural areas, excoriated nodules and excoriation marks with erosions, oozing and crusts Face has diffuse infiltrated erythema with fine desquamation. Presence of xeroderma No burrows on hands or genitals Good general status, with no lymphadenopathy or fever	Widespread AD with many excoriations; prurigo nodularis-type lesions on calves; recurrent alopecia on both sides of scalp	Very dry skin, scaling and redness on upper limbs (medial) and shoulders. Scratch marks, dry skin and erythema on upper limbs, shoulders and neck; less-pronounced erythema at flexural sites of arms; scaling; no oozing; minimal lichenification at flexures of left arm. Eczema has started at flexural sites
<i>Patient history</i> Has had AD since mid-childhood; resolution at age 12 years; recurrence at age 17 years	Has not experienced prolonged resolution of dermatitis. Has had food allergies, asthma, allergic rhinitis and allergic conjunctivitis since childhood. Reports worsening of dermatitis during both summer and winter Has been referred owing to complete loss of control of AD for a prolonged period	Experienced mild AD and asthma during childhood; seemed to be growing out of it Eczema (severe, generalized) reappeared last year when hand eczema started	Has had AD since infancy. Often experiences severe eczema, which has been treated with antibiotics several times Had a type I egg and milk allergy in early childhood	Has had alopecia areata at different time-points	Had allergic rhinitis when young, but does not recollect experiencing skin diseases
<i>Family history of atopy</i> None	Several first-degree relatives have allergic disease	Mother had allergic rhinitis	Mother and father with allergic rhinitis	Brother also has AD	Brother has asthma and AD
<i>Treatment history</i> Tried many topical treatments including calcineurin inhibitors, 8 weeks of UV therapy and 3 weeks of a low dose of azathioprine 6 years ago, which had minimal effect Currently using weak or moderate TCS intermittently	Topical anti-inflammatory (including high-strength TCS) and phototherapy; infections have mandated IV antibiotics Currently using moderate TCS intermittently	Emollient plus weak and moderate TCS, which were previously effective at controlling her AD	Emollients, topical steroids, UVB therapy and heliotherapy in Southern Europe as a child	Topical corticosteroids. Has also tried tacrolimus ointment, mainly on face. Used cyclosporine for 3 months with good response, but was stopped because of pneumonia. Has tried methotrexate twice, last time for almost a year, but response was not very good	Self-medicated with moisturizers
<i>Comorbidities</i> No other past major conditions No other past major conditions	No other past major conditions No psychiatric diseases in the past	Asthma and AD during childhood; no current medication	Allergic rhinitis; smoker	Asthma, allergic rhinitis (pollens, dogs and cats) and nasal polyposis. Is showing signs of depression from burden of itch, pain and inability to get control of his condition, although he has received no formal diagnosis. No other long-term diseases	Coxarthrosis, obesity and hypertension (medicated with ACE inhibitor enalapril maleate and paracetamol for >10 years)
This patient presentation is typical of patients with moderate-to-severe, late-onset AD (consensus statement for voting)					
Agreed, 100%			Agreed, 100%		
These cases reflect the spectra of the most typical presentations of adult moderate-to-severe AD seen in clinics			Agreed, 100%		
Agreed, 100%					

ACE: angiotensin-converting enzyme; AD: atopic dermatitis; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; HEES: Hand Eczema Extent Score; TCS: topical glucocorticosteroids; UV: ultraviolet.

Table II. Diagnostic work-up statements for expert voting

Case 1 Moderate-to-severe head and neck dermatitis	Case 2 Moderate-to-severe AD with type I allergies	Case 3 Moderate-to-severe AD with hand eczema	Case 4 Moderate-to-severe AD with recurrent infections	Case 5 Moderate-to-severe lichenified AD with severe itch	Case 6 Moderate-to-severe, late-onset AD
<i>Conduct patch tests to identify possible contact allergies to ingredients in cosmetics, emollients and other topical treatments in cases of difficult-to-control disease</i>					
Agreed, 93%	No consensus reached (Agreed, 43%; neither agreed nor disagreed, 14%; disagreed, 43%)	Not considered relevant for case 3	Not considered relevant for case 4	No consensus reached (Agreed, 60%; neither agreed nor disagreed, 27%; disagreed, 13%)	No consensus reached (Agreed, 47%; neither agreed nor disagreed, 27%; disagreed, 27%)
Patch testing should not be part of a primary work-up in this patient type					
Agreed, 93%	No consensus reached (Agreed, 50%; neither agreed nor disagreed, 21%; disagreed, 29%)	Not considered relevant for case 3	Not considered relevant for case 4	No consensus reached (Agreed, 53%; neither agreed nor disagreed, 13%; disagreed, 33%)	No consensus reached (Agreed, 47%; neither agreed nor disagreed, 0%; disagreed, 53%)
<i>Conduct an exposure analysis</i>					
Not considered relevant for case 1	Not considered relevant for case 2	If contact eczema is suspected, patients' work and home environment and hobbies/interests should be assessed for exposure to possible contact allergens and irritants to enable the patient to avoid them Agreed, 100% If applicable, inspection and testing should be performed Agreed, 100%	Not considered relevant for case 4	Not considered relevant for case 5	Not considered relevant for case 6
<i>Evaluation of home and workplace environment</i>					
Not considered relevant for case 1	Not considered relevant for case 2	Environmental risk assessment: provide information on how to avoid identified allergens and irritants in the workplace and on the consequences of exposure, which can be provided to the employer Agreed, 100%	Not considered relevant for case 4	Not considered relevant for case 5	Consider home assistance for elderly/impaired patients Agreed, 80%
<i>Conduct a standard work-up for type I aero-allergens</i>					
No consensus reached (Neither agreed nor disagreed, 29%; disagreed, 72%)	No consensus reached (Agreed, 71%; neither agreed nor disagreed, 7%)	Disagreed 80%	No consensus reached (Agreed, 20%; neither agreed nor disagreed, 7%; disagreed, 73%)	No consensus reached (Agreed, 20%; neither agreed nor disagreed, 33%; disagreed, 47%)	Not considered relevant for case 6
<i>Conduct a standard work-up for food allergens</i>					
Disagreed, 100%	Agreed, 100%	Disagreed, 87%	No consensus reached (Neither agreed nor disagreed, 33%; disagreed, 67%)	No consensus reached (Neither agreed nor disagreed, 33%; disagreed, 67%)	Not considered relevant for case 6
<i>Further investigation, including determination of potential skin infections and differential diagnoses</i>					
Conduct skin microscopy and/or cultures for <i>Malassezia furfur</i> colonization Disagreed, 86%	Not considered relevant for case 2	Not considered relevant for case 3	Attempt to identify the organism causing recurrent infection starting with skin swabs for bacterial testing Agreed, 80%	Not considered relevant for case 5	Conduct additional blood tests, such as blood glucose and thyroid hormone, to help exclude other possible conditions Agreed, 93%
Conduct <i>M. furfur</i> -specific IgE/total IgE test to determine the sensitization of <i>M. furfur</i> No consensus reached (Agreed, 50%; neither agreed nor disagreed, 14%; disagreed, 36%)	Not considered relevant for case 2	Not considered relevant for case 3	Consider viral testing if clinical suspicion of herpes Agreed, 100%	Not considered relevant for case 5	Perform skin biopsy if lymphoma or another differential diagnosis is suspected Agreed, 100%
<i>Refer to other specialists</i>					
Not considered relevant for case 1	Consider referral to an allergist/pulmonologist/ ophthalmologist No consensus reached (Agreed, 57%; neither agreed nor disagreed, 36%; disagreed, 7%)	If appropriate, consider referral to an allergist/occupational health specialist Agreed, 93%	Consider referral to an allergist or another specialist No consensus reached (Agreed, 20%; neither agreed nor disagreed, 20%; disagreed, 60%)	Refer patient to a psychologist for assessment No consensus reached (Agreed, 73%; neither agreed nor disagreed, 27%)	If appropriate, consider referral to an allergist/ endocrinologist or another specialist if there are underlying conditions requiring assessment and treatment Agreed, 100%
<i>Actively explore type I and type IV allergic comorbidities</i>					
Not considered relevant for case 1	Agreed, 86%	No consensus reached (Agreed, 67%; neither agreed nor disagreed, 20%; disagreed, 13%)	No consensus reached (Agreed, 47%; neither agreed nor disagreed, 33%; disagreed, 20%)	Not considered relevant for case 5	Not considered relevant for case 6

At a minimum, the severity of disease should be assessed based on symptoms, skin examination and impact on the patient. **Agreed, 100%**.
If possible within your clinic, measure disease severity using accepted tools for skin disease assessment (e.g. EASI), symptoms (e.g. NRS, VAS) and QoL assessment (e.g. DLQI). **Agreed, 79%**.
Test for filaggrin gene mutations if the test is available, e.g. to guide patient education about the aetiology and prognosis of their disease and subsequent consequences such as childbirth or inheritance. **Disagreed, 93%**.

AD: atopic dermatitis; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; NRS: numerical rating scale; QoL: quality of life; VAS: visual analogue scale.

Table III. Targeted patient education statements for expert voting

<p>Targeted patient education and support is a critical first step in any management plan; this may include some or all of the following:</p> <ul style="list-style-type: none"> • Educate patients about washing and hygiene habits relevant to the condition and to assist with self-management. • Advise patients on how to apply treatment, such as topical steroids or topical calcineurin inhibitors and how to self-manage their condition, where possible. • Advise patients on daily emollient application. • Advise patients on relevant adjuvant approaches, such as wearing gloves during the night, keeping nails short and wearing pyjamas. • Question and counsel patient about existing medication usage and adherence to prescribed topical treatment. • Address relevant lifestyle or medical factors, e.g. pregnancy and pregnancy planning must be discussed with the patient. • If a patch or prick test is positive, discuss relevant allergens and how to avoid them. • Explore potential depression/anxiety/psychiatric conditions both related and unrelated to patients' dermatitis. • Some patients may benefit from a referral for psychological or psychiatric treatment. • Agreed, 93%

DISCUSSION

The consensus discussion approach used to map expert opinions was chosen owing to the lack of coherent agreement guidance on the clinical management of AD in adults in Denmark, Finland, Norway and Sweden. Expert insight used a patient-specific approach to review the typical practice of contemporary diagnostic work-up and AD treatment approaches in Nordic countries.

Diagnostic work-up (Table II)

AD scoring tools. Experts were in full agreement (100%) on the assessment of disease severity; they agreed that a robust clinical assessment was necessary using symptoms and skin examination to ascertain the impact on the patient. Consensus was also reached on the importance of using accepted scoring tools for assessing different aspects of AD (79% agreed); including, but not limited to, EASI, POEM and SCORAD for disease severity; the numerical rating scale or visual analogue scale for symptoms; and the DLQI for HRQoL assessment. Although the composite use of subjective and objective scoring systems is recommended in the European guidelines on AD assessment (11), experts did not feel that it was always practical to use the scoring tools during routine consultations and instead relied on their clinical experience for assessing many aspects of the disease. They also believed that the use of scoring systems should not exclude a simultaneous holistic view. Furthermore, they felt that the importance of regular, long-term measurements should be emphasized to physicians: disease activity can vary greatly between visits, hence it is essential to have a detailed timeline of disease activity including severity score and the duration of symptom-free periods. Measurements/assessments should be carried out for 3–6 months, and for assessment of long-term control, for one year (or longer).

Additional tests for AD work-up. Experts reached a consensus (93%) that testing for filaggrin gene mutations was not necessary for patient education on disease aetiology, prognosis and consequences, such as inheritance. Only in

case 1 (moderate-to-severe head and neck dermatitis) was it agreed (93%) that patch testing should be performed to identify possible contact allergies to ingredients in cosmetics, emollients and other topical treatments. Patch tests were considered too onerous for routine testing in patients with AD, but the experts agreed that they should be performed at the physician's discretion, for example for patients who have not had previous patch tests and/or where a clinical suspicion of complicating allergic contact dermatitis could not be ruled out, or in cases of treatment failure; typically with generalization of eczema or spread outside the traditional areas. Patch tests may also be considered for patients with chronic AD, or as with case 3 (moderate-to-severe AD with hand eczema) where the aetiology of hand eczema could be mixed.

Similarly, skin prick tests or measurements of specific IgE were not considered necessary as part of routine testing in moderate-to-severe adult AD; however, if there is suspicion of a type I respiratory, gastrointestinal or ocular allergy (e.g. in case 2 (moderate-to-severe AD with type I allergies)), skin prick tests or specific IgE testing should be initiated by the dermatologist. In patients with a relevant history, similar to case 3 (moderate-to-severe AD and hand eczema), physicians may perform a skin prick test with foods to confirm overlying contact urticarial and suspected protein contact dermatitis.

The panel's recommendations for the use of standard allergen work-up varied between cases, reflecting the difference in the predominant underlying disease process. For example, testing for food allergens in case 2 (moderate-to-severe AD with type I allergies) was mandated in instances where this could be a contributing aggravating factor of AD (100% agreed). In case 3 (moderate-to-severe AD with hand eczema), experts reached a consensus that neither aero nor food allergens need to be tested in instances where they are unlikely to be an underlying trigger (80% and 87%, respectively), but there was a full consensus (100% agreed) for performing exposure analyses and environmental inspection for contact allergens in patients with hand eczema.

Evaluation before systemic treatment. The pre-treatment evaluations used before systemic treatment were found to be heterogeneous across these Nordic countries: chest X-rays may be performed before commencing methotrexate, thiopurine methyltransferase genotype and phenotype testing may be performed before azathioprine use, and it is recommended, but not mandatory, that both creatinine filtration rate and blood pressure measurement should be performed before cyclosporine use.

Infection control and differential diagnosis. *Staphylococcus aureus* colonization is frequent in lesional skin of patients with AD and can be an important factor in aggravating skin lesions (22). If a patient presents with widespread infected AD with oozing dermatitis, the clinician would usually immediately commence appropriate oral antibiotic treatment (e.g. dicloxacillin/flu-

Table IV. Treatment goal and approach statements for expert voting

	Case 1 Moderate-to-severe head and neck dermatitis	Case 2 Moderate-to-severe AD with type I allergies	Case 3 Moderate-to-severe AD with hand eczema	Case 4 Moderate-to-severe AD with recurrent infections	Case 5 Moderate-to-severe lichenified AD with severe itch	Case 6 Moderate-to-severe, late-onset AD
<i>Goals of treatment</i>	To stabilize dermatitis at the lowest level and reduce the symptoms of greatest concern to the patient Agreed, 100%	To stabilize dermatitis at the lowest level and reduce the symptoms of greatest concern to the patient Agreed, 100%	To maintain barrier function to control symptoms like itch or pain and stabilize AD Agreed, 100% To control hand dermatitis and re-establish function to enable the return to the workplace/labour market Agreed, 93%	To stabilize dermatitis at the lowest level, control and prevent infections and reduce the symptoms of greatest concern to the patient Agreed, 100%	To stabilize dermatitis at the lowest level, reduce the symptoms of itch and improve sleep and QoL Agreed, 100%	To stabilize dermatitis at the lowest level and reduce the symptoms of greatest concern to the patient, including improvement in QoL, reduction of itch and improvement of sleep Agreed, 100%
<i>Initial therapy</i>	Daily application of appropriate TCS to different skin areas Example of an appropriate treatment regimen would be a moderate TCS applied to face and potent TCS applied to neck and trunk Agreed, 100%	Daily application of appropriate TCS for different skin areas. Examples of appropriate treatment regimens would be: (i) Potent TCS applied to all body parts except armpits, crotch and face until AD has resolved (for ≤4 weeks) (ii) Moderate TCS 1 x daily applied to armpits, crotch and face for ≥1 week until AD has resolved (for ≤4 weeks) <i>Consensus not reached</i> (Agreed, 40%; neither agreed nor disagreed, 27%; disagreed, 33%)	Daily application of appropriate TCS. Example of an appropriate treatment regimen would be an extra potent TCS applied 1 x daily to hands until eczema has resolved (for ≤4 weeks) Agreed, 80% Initial recommended therapy for the rest of the body is daily application of appropriate TCS for different skin areas Examples of appropriate treatment regimens would be: (i) Potent TCS applied to eczema lesions on all body parts except face, genitals and armpits (ii) Moderate TCS applied to eczema lesions on face, genitals and armpits Agreed, 80%	Oral antibiotics (dicloxacillin/flucloxacillin/cephalexin) with emollient (≥2x daily) and TCS applied to eczema lesions 1 x daily for 1-2 weeks and thereafter every other day. When eczema is under control, consider "weekend therapy" Examples of appropriate treatment regimens would be: (i) Potent TCS applied to eczema lesions on all body parts except face, genitals and armpits (ii) Moderate TCS applied to eczema lesions on face, genitals and armpits Agreed, 87%	Occlusive therapy with a potent or IV TCS to control inflammation and itch Agreed, 87%	Daily application of appropriate TCS for different skin areas. Examples of appropriate treatment regimens would be: (i) Potent TCS applied to all body parts except armpits, crotch and face until AD has resolved (for ≤4 weeks) Agreed, 100% (ii) Moderate TCS applied 1 x daily to armpits, crotch and face for 1 week until AD has resolved (for ≤4 weeks) Agreed, 93%
Add 2% ketoconazole shampoo 2 x weekly for the first week and then weekly thereafter <i>Consensus not reached</i> (Agreed, 73%; neither agreed nor disagreed, 7%; disagreed, 20%)						
<i>TCl would be a safe and effective alternative to TCS in this patient</i>		Consider TCI if patient has periorbital dermatitis, may have used TCS inappropriately or does not wish to use TCS Agreed, 93%	Not considered relevant for case 3	Not considered relevant for case 4	No <i>consensus reached</i> (Agreed, 60%; neither agreed nor disagreed, 20%)	Not considered relevant for case 6
<i>Follow-up, tapering and maintenance</i>		TCS treatment commences				
Patient should be assessed 2-3 weeks after TCS treatment commences		No <i>consensus reached</i> (Agreed, 40%; neither agreed nor disagreed, 27%; disagreed, 33%)	No <i>consensus reached</i> (Agreed, 33%; neither agreed nor disagreed, 40%; disagreed, 27%)	Not considered relevant for case 4	Not considered relevant for case 5	No <i>consensus reached</i> (Agreed, 40%; neither agreed nor disagreed, 33%; disagreed, 27%)
Not considered relevant for case 1		Agreed, 100%	Not considered relevant for case 3	Not considered relevant for case 4	Not considered relevant for case 5	Agreed, 100%
<i>The frequency of TCS/TCI application should be tapered to 2 x weekly after the initial treatment period if AD is under control</i>			Not considered relevant for case 3	Not considered relevant for case 4	Not considered relevant for case 5	Agreed, 100%
Agreed, 87%			Not considered relevant for case 3	Not considered relevant for case 4	Not considered relevant for case 5	Agreed, 100%
<i>For ongoing maintenance of stable chronic AD, TCS/TCI twice weekly to prevent acute flares is recommended</i>		Not considered relevant for case 2	Not considered relevant for case 3	Not considered relevant for case 4	Not considered relevant for case 5	Agreed, 100%
Agreed, 93%			Not considered relevant for case 3	Not considered relevant for case 4	Not considered relevant for case 5	Agreed, 100%
<i>If treatment response to initial therapy is suboptimal and phototherapy is practical/convenient for the patient, consider adding phototherapy to induce remission</i>			No <i>consensus reached</i> (Agreed, 53%; neither agreed nor disagreed, 7%; disagreed, 40%)	No <i>consensus reached</i> (Agreed, 67%; neither agreed nor disagreed, 27%; disagreed, 7%)	No <i>consensus reached</i> (Agreed, 73%; neither agreed nor disagreed, 20%; disagreed, 7%)	Agreed, 87%
No <i>consensus reached</i> (Agreed, 67%; neither agreed nor disagreed, 20%; disagreed, 13%)			No <i>consensus reached</i> (Agreed, 73%; neither agreed nor disagreed, 20%)	No <i>consensus reached</i> (Agreed, 67%; neither agreed nor disagreed, 27%; disagreed, 7%)	No <i>consensus reached</i> (Agreed, 73%; neither agreed nor disagreed, 20%; disagreed, 7%)	Agreed, 87%
The selection of treatment should be dictated by past treatment experience, contraindications, comorbidities and patient preference. Agreed, 100% . If treatment response to topical treatment with or without phototherapy is suboptimal, not tolerated or initial treatments are contraindicated, initiate and optimize systemic therapy. Agreed, 100% . Optimize treatment with your chosen systemic treatment and allow 3 months on the maximum dose for the full treatment effect to develop before considering switching. Agreed, 100% .						

AD: atopic dermatitis; QoL: quality of life; TCI: topical calcineurin inhibitors; TCS: topical glucocorticosteroids.

Table V. Systemic treatment options for expert voting

	Case 1 Moderate-to-severe head and neck dermatitis	Case 2 Moderate-to-severe AD with type I allergies	Case 3 Moderate-to-severe AD with hand eczema	Case 4 Moderate-to-severe AD with recurrent infections	Case 5 Moderate-to-severe lichenified AD with severe itch	Case 6 Moderate-to-severe, late-onset AD
Treatments selected as any line of treatment (alphabetical order)	Azathioprine (±oral prednisolone) Cyclosporine Dupilumab Methotrexate	Azathioprine Cyclosporine Dupilumab Methotrexate	Alitretinoin Azathioprine Cyclosporine Dupilumab Methotrexate (±oral prednisolone)	Azathioprine Cyclosporine Dupilumab Methotrexate Mycophenolate mofetil	Azathioprine (±oral prednisolone) Cyclosporine Dupilumab Methotrexate (±oral prednisolone) Mycophenolate mofetil (± oral prednisolone)	Azathioprine (±oral prednisolone) Cyclosporine Dupilumab Methotrexate Mycophenolate mofetil
Trends in treatment choice	First-line: methotrexate (53.3%) Second-line: azathioprine, cyclosporine and methotrexate selected with equal frequency (26.7% each) Third-line: dupilumab (66.7%) Azathioprine plus oral prednisolone was selected as first- or second-line by <7% of experts	First-line: cyclosporine (53.3%) Second-line: azathioprine (35.7%) Third-line: dupilumab (71.4%)	First-line: methotrexate (40%) Second-line: azathioprine (33.3%) Third-line: azathioprine and dupilumab (both 26.7%) Methotrexate plus oral prednisolone was selected as second-line by <7% of experts	First-line: methotrexate (53.3%) Second-line: cyclosporine (33%) Third-line: dupilumab (66.7%) Mycophenolate mofetil was selected as second-line by <7% of experts	First-line: cyclosporine (40%) Second-line: azathioprine (33.3%) Third-line: dupilumab (53.3%) Experts chose more options with oral prednisolone bridging in case 5 than other cases; however, percentage of experts using oral prednisolone bridging was small (<7–13.3%)	First-line: methotrexate (66.7%) Second-line: azathioprine or methotrexate selected with equal frequency (33%) Third-line: dupilumab (66.7%) Mycophenolate mofetil was selected as third-line by <7% of experts

AD: atopic dermatitis.

cloxacillin/cephalexin) and collect material for culture. Treatment could be adjusted if the organism is found to be resistant. Identification of infection was considered very important in case 4 (moderate-to-severe AD with recurrent infections; 80–100% agreed), particularly if the patient is starting antibiotics and systemic treatment simultaneously.

Consensus was reached on considering a differential diagnosis for case 6 (moderate-to-severe, late-onset AD) where there was a risk of misdiagnosing cutaneous T-cell lymphoma (93–100% agreed); suspected lymphoma should be investigated with repeated skin biopsies, as well as blood and bone marrow tests, and potential overlying or competing allergic contact dermatitis should be excluded with patch testing.

Allergic comorbidities and referrals. Patient referral to other specialists, such as ophthalmologists or pulmonologists, was not considered to be part of routine patient management. Instead, this should be based on the presentation of specific clinical symptoms, such as ocular or pulmonary manifestations. The experts agreed that patient history should include relevant allergic comorbidities, such as conjunctivitis, asthma and rhinoconjunctivitis; dermatologists should recognize exacerbation of symptoms that are likely to be caused by allergens, such as underlying grass pollen or another (type I) aero-allergen that can aggravate AD symptoms if the individual is exposed (23).

Experts agreed that, if appropriate, dermatologists should refer patients with moderate-to-severe AD with hand eczema (93% agreed) or moderate-to-severe, late-onset AD (100% agreed) to other specialists, such as an allergist or occupational health specialist, if local conditions lead to challenges in managing and diagnosing these patients. Experts agreed (86%) that physicians should evaluate allergic comorbidities in patients with moderate-to-severe AD with type I allergies because al-

lergic comorbidities may have worsened their AD over a long period of time.

Targeted patient education statements and treatment goals and approaches (Tables III–IV)

Patient education, treatment approaches and goals. Patient education has proven to be effective in increasing treatment adherence and HRQoL in AD (24). Consensus was reached (93% agreed) on the importance of targeted patient education and patient support in any management plan. Table III shows a comprehensive list of education points, which may vary depending on the patient. Daily use of emollients was considered an important step in managing all cases of AD.

The experts strongly agreed that the selection of treatment should be dictated by past treatment experience, contraindications, comorbidities and patient preference (100% agreed; Table IV), and that if treatment response to topical therapy with or without phototherapy is suboptimal or not tolerated or initial treatments are contraindicated, systemic therapy should be initiated and optimized in patients with moderate-to-severe AD.

The ultimate goal of AD treatment is for patients to live a fulfilled life that is relatively unrestricted by AD. This goal is patient-specific and should address the symptoms that patients perceive to be the worst, such as cosmetic concerns, itchy or painful skin and poor-quality sleep. Table IV shows the treatment goal and approach statements. Consensus was reached (100% agreed) on the goals of treatment: to stabilize dermatitis at the lowest level and reduce the symptoms of greatest concern to the patient (for cases 1, 2 and 4–6), including reducing itch, improving sleep and HRQoL for patients with moderate-to-severe lichenified AD with severe itch and/or moderate-to-severe, late-onset AD; and to prevent infections in patients with moderate-to-severe AD with

recurrent infections. Consensus on 2 treatment goals for patients with moderate-to-severe AD with hand eczema was also agreed (93%): “to maintain barrier function to control symptoms such as itch or pain and stabilize AD” and “to control hand dermatitis and re-establish function to enable the return to the workplace/labour market”.

Initial treatment of AD. The treatment approach statements are shown in Table IV. TCS are well-recognized as the first-line anti-inflammatory treatment for managing AD in children and adults (11). The consensus upheld the recommendations of the European guidelines to use TCS for treating the initial phase of AD exacerbation in the majority of these case profiles (80–100% agreed) (11); however, in case 2 (moderate-to-severe AD with type I allergies), consensus was not reached. In relevant cases, consensus was reached on tapering topical treatment from once-daily to a twice-weekly application (87–100% agreed). It was stressed that the TCS potency should always be adjusted to the anatomical region that was treated. Consensus was also reached (80% agreed) on the short-term use of oral antibiotics (dicloxacillin/flucloxacillin/cephalexin) to control moderate-to-severe AD with recurrent infections. There was no consensus for the use of 2% ketoconazole shampoo in patients with moderate-to-severe head and neck dermatitis or the use of phototherapy, with the exception of moderate-to-severe, late-onset AD, where phototherapy would be considered (87% agreed).

In agreement with the European guidelines, experts recommended exercising caution with the use of TCS on the face (11). TCS may be responsible for the “red face” described in case 2, and therefore should be restricted to a maximum use of 2 weeks. It was noted that TCI may be the preferred initial topical treatment alternative to TCS (rather than the second-line treatment) and may be preferable to TCS for long-term maintenance; however, TCI and phototherapy should not be combined (25). Consensus was not reached on how long a patient should be treated with TCS before assessing response; however, the panel generally thought that 3 weeks was not sufficient and that 4–6 weeks would be more appropriate.

Phototherapy and balneotherapy. The need for phototherapy was not universally agreed between the experts and their views may have been influenced by variation in treatment culture in these Nordic countries, as well as individual clinical experience and practicality for the patient (e.g. travel distance to the treatment centre). During discussions, experts agreed that balneotherapy (baths including potassium permanganate and bleach baths) would be an appropriate treatment for patients with moderate-to-severe AD with recurrent infections (case 4), but it was emphasized that the evidence level is poor (26, 27).

Systemic therapy (Table V). Systemic therapies commonly used for the treatment of moderate-to-severe AD include methotrexate, cyclosporine, azathioprine,

mycophenolate mofetil, oral prednisolone and dupilumab (11).

In Denmark, to be considered eligible for dupilumab treatment, adult patients with AD must have tried and failed (or not tolerated/been ineligible for) 2 conventional systemic immunosuppressant treatments (e.g. methotrexate and azathioprine) and also have an EASI score >16, and DLQI >10 or POEM score >16.

In Finland, dupilumab is reimbursed in patients with severe AD, and in whom conventional systemic treatment has insufficient efficacy, is contraindicated, or is not suitable.

Although dupilumab has been approved in Norway, governmental reimbursement has not yet been granted, and it can only be prescribed in individual patients at university hospitals. Furthermore, in Norway, dupilumab is reimbursed on a regional level so the department initiating the treatment covers the costs, and consequently, few patients in Norway currently receive dupilumab treatment.

In Sweden, dupilumab is reimbursed for patients with severe AD, who, because of the insufficient efficacy of conventional systemic treatment or other medical reasons, lack additional treatment options.

The length of time a patient should try a given systemic therapy before escalating the dose or switching treatment if there is limited efficacy varies. Experts recommended that systemic treatment should be optimized and that patients should be maintained for 3 months on the maximum dose for the full treatment effect to develop and to ascertain adherence to treatment before considering switching (100% agreed); this view was consistent across all cases.

No consensus was reached for first-, second- or third-line systemic treatment in any of the cases (Table V). Countries in the Nordic region have different cultures and traditions of treatment practice, as well as reimbursement schemes, which may explain the lack of agreement on treatment (Figs S1–S6¹). The experts did not identify a role for oral prednisolone as a single agent for the management of moderate-to-severe AD, although some clinicians may occasionally use it as part of a bridging regimen in selected patients. Mycophenolate mofetil (including with prednisolone bridging) is rarely used in any line of therapy.

For case 1 (moderate-to-severe head and neck dermatitis), a high EASI score was considered important for clinical decision-making regarding systematic treatment; however, experts highlighted that a high EASI score may not be necessary to justify switching from one systemic treatment to another in patients with moderate AD who continue to experience symptoms.

For case 2 (moderate-to-severe AD with type I allergies), identifying a systemic AD treatment that could also treat the patient’s allergic comorbidities would be a driver in selecting a systemic treatment.

For case 3 (moderate-to-severe AD with hand eczema), treatment decisions would be driven by clinical practice and drug efficacy and safety, in addition to country-specific reimbursement. The patient was a 20-year-old woman; thus age and childbearing potential were also important drivers. Alitretinoin, mycophenolate mofetil and methotrexate are teratogenic and are therefore contraindicated in pregnancy; systemic corticosteroid and cyclosporine treatment can be used during pregnancy; there are conflicting data for azathioprine use in pregnancy; and data are not yet available for dupilumab use in pregnancy (11).

Systemic treatment decisions for case 5 (moderate-to-severe lichenified AD with severe itch) would be driven by clinical practice, drug efficacy, country-specific reimbursement and safety; however, they would also be influenced by previous treatment history, and this patient's previously unsuccessful systemic treatments would influence the subsequent treatment choice.

Decisions on systemic treatment for case 6 (moderate-to-severe, late-onset AD) would be driven by a variety of factors, including safety, clinical practice, drug efficacy and country-specific reimbursement. With late-onset AD, patient age is also an important factor; nephrotoxicity from cyclosporine use is more common in elderly patients (11), and there is a risk of worsening of an underlying and unrecognized cutaneous T-cell lymphoma (28). The cost of medication may be a further consideration; for example, in some countries, methotrexate may be an attractive option as it is an affordable treatment.

Systemic treatment by Nordic country (Figs S1–S6¹). Across the patient example cases, the experts most frequently recommended first-line methotrexate, cyclosporine and azathioprine. In Denmark, methotrexate is the preferred first-line treatment for AD, whereas in Norway, cyclosporine tends to be preferred; the picture was less clear in Finland and Sweden.

The second-line treatments most frequently selected for AD were azathioprine in Denmark and dupilumab in Sweden, whereas second-line treatment selection tended to be more varied in Norway and Finland.

Local differences in treatment culture may also be associated with marketing authorization and reimbursement in AD. For each patient, the relative benefits and limitations for any systemic treatment should be weighed carefully, taking into account the patient's preferences. As highlighted in this discussion, there are different preferences in these Nordic countries, yet they are all in accordance with international guidelines for the treatment of AD. The experts commented that, if a biologic such as dupilumab was chosen for the second-line treatment of AD, there may not be an attractive third-line option; however, if a combination of a systemic immunosuppressive plus a biologic was available, this could be a feasible alternative to dupilumab as a single agent.

Study limitations

This modified Delphi consensus approach had a number of limitations. Firstly, the profiling of cases was based on the Steering Committee's descriptions of clinical presentation and their experience of diagnosing AD rather than any evidence base that defines specific patient "phenotypes". Secondly, this study was limited in its ability to produce Nordic-wide recommendations on the use of systemic treatment because of the small sample size of clinical experts and varying local clinical practice and reimbursement rules within and between these Nordic countries.

Conclusion

The results of this first meeting among Nordic AD experts show that many different clinical approaches within the bounds of international guidelines, each with individual merits, are currently utilized. Marked heterogeneity in the approaches to diagnostic work-up and systemic treatment choices in moderate-to-severe AD exists across the Nordic countries, and this is likely to be influenced by local treatment culture and reimbursement guidelines.

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