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ORIGINAL ARTICLE

Systemic treatment of children and adolescents with atopic dermatitis aged ≥2 years: a Delphi consensus project mapping expert opinion in Northern Europe

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Abstract

Background Paediatric atopic dermatitis (AD) can be burdensome, affecting mental health and impairing quality of life for children and caregivers. Comprehensive guidelines exist for managing paediatric AD, but practical guidance on using systemic therapy is limited, particularly for new therapies including biologics and Janus kinase (JAK) inhibitors, recently approved for various ages in this indication.

Objectives This expert consensus aimed to provide practical recommendations within this advancing field to enhance clinical decision-making on the use of these and other systemics for children and adolescents aged ≥2 years with moderate-to-severe AD.

Methods Nineteen physicians from Northern Europe were selected for their expertise in managing childhood AD. Using a two-round Delphi process, they reached full or partial consensus on 37 statements.

Results Systemic therapy is recommended for children aged ≥2 years with a clear clinical diagnosis of severe AD and persistent disease uncontrolled after optimizing non-systemic therapy. Systemic therapy should achieve long-term disease control and reduce short-term interventions. Recommended are cyclosporine A for short-term use (all ages) and dupilumab or methotrexate for long-term use (ages ≥6 years). Consensus was not reached on the best long-term systemics for children aged 2–6 years, although new systemic therapies will likely become favourable: New biologics and JAK inhibitors will soon be approved for this age group, and more trial and real-world data will become available.

Conclusions This article makes practical recommendations on the use of systemic AD treatments for children and adolescents, to supplement international and regional guidelines. It considers the systemic medication that was available

MdG, SRJ and MLAS contributed equally to this work.

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for children and adolescents with moderate-to-severe AD at the time this consensus project was done: azathioprine, cyclosporine A, dupilumab, methotrexate, mycophenolate mofetil and oral glucocorticosteroids. We focus on the geographically similar Northern European countries, whose healthcare systems, local preferences for AD management and reimbursement structures nonetheless differ significantly.

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Conflicts of interest

AMvTvS is an advisor for AbbVie, LEO Pharma, Novartis and UCB Pharma and an advisor and speaker for Sanofi Genzyme. BKK is a speaker for ALK, AstraZeneca, Sanofi Genzyme and the Norwegian Medical Association. She has stock or stock options in Juvenilia AS, Majamed AS and Barneleg1. CV is an advisor, consultant or investigator for AbbVie, Sanofi Genzyme, Novartis, LEO Pharma, MSD, and Pfizer. He has received research grants from Pfizer, LEO Pharma and Novartis. EKJ has received speaker honoraria and/or been a consultant for Sanofi Genzyme, LEO Pharma, ACO, Novartis, AbbVie. HO is a consultant for Pfizer. JMM is an advisor, consultant, speaker or investigator for AbbVie, Eli Lilly, LEO Pharma, Orion Pharma and Sanofi Genzyme. JPT is an advisor, consultant, speaker and investigator for AbbVie, Arena Pharmaceuticals, Pfizer, LEO Pharma, Regeneron, Sanofi Genzyme, Almirall, ASLAN, OM-85 and Coloplast. He has received research grants from Regeneron, Pfizer and Sanofi Genzyme. KD is an advisor, consultant, speaker or investigator for Sanofi Genzyme, LEO Pharma and AbbVie. She has received grants from LEO Pharma and AbbVie. LH is an advisor, consultant, speaker or investigator for Novartis, Eli Lilly, LEO Pharma, AbbVie, Sanofi Genzyme, Orion Pharma and Pfizer. MD is an advisor, consultant or investigator for AbbVie, Sanofi Genzyme, Regeneron, LEO Pharma, Pfizer, Arena Pharmaceuticals, La Roche Posay, Novartis, Almirall, Pierre Fabre and Eli Lilly. She has received grants from LEO Pharma, AbbVie, Eli Lilly, Regeneron, Sanofi Genzyme and Pfizer. MdG is an advisor, consultant, speaker or investigator for Sanofi Genzyme, LEO Pharma and Eli Lilly. She had received grants from Sanofi Genzyme and Regeneron. MLAS is an advisor, consultant, speaker and/or investigator for AbbVie, Pfizer, LEO Pharma, Regeneron, Sanofi Genzyme, Eli Lilly and Galderma. She has received grants from Regeneron and Sanofi Genzyme, Novartis and Pfizer. PDG is an advisor, speaker, consultant or investigator for AbbVie, Janssen, LEO Pharma, Novartis, UCB Pharma, Amgen, Eli Lilly, Galderma, BMS, Meda, Maruho, Flen, Menarini, Almirall, Boehringer Ingelheim and Viatris. SRJ is an advisor or speaker for, or has received honoraria from, Novartis, Sanofi Genzyme, Janssen and LEO Pharma. He has received grants from Pierre Fabre. TA is an advisor, consultant, speaker and/or investigator for AbbVie, Pfizer, LEO Pharma, Sanofi Genzyme and Eli Lilly. VE is a speaker for Sanofi Genzyme. All other authors have no conflicts of interest to declare.

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This Delphi project was funded by Sanofi Genzyme. The expert panel was invited by the study sponsor but remained independent, having not been appointed by any national dermatological society or regulatory authority from any of the respective countries.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease resulting in itchy and painful skin, which reduces the quality of life.[1] Most children experience mild disease, but for others, AD substantially impairs their quality of life and that of their families and caregivers; therefore, AD should be considered a serious disease with systemic manifestations and long-term sequelae.[2,3] AD is an early step along the atopic march and can predate the development of other allergic comorbidities, including food allergy, rhino-conjunctivitis and asthma.[2,4–6] AD increases the risk of infections and associates with some autoimmune disorders and psychiatric diseases.[7,8]

Managing moderate-to-severe AD in children involves trigger avoidance and daily use of emollients, intermittent use of topical corticosteroids (TCS) and calcineurin inhibitors, phototherapy in some cases and systemic immunosuppressants.[9–11] Many children achieve good disease control with these agents, but a significant minority experiences side effects and suboptimal efficacy.[9] Furthermore, dermatologists and paediatricians may hesitate to start systemic or biologic therapy in children, owing to the lack of experience in this age group. Existing data on the long-term safety of these agents for young children are insufficient and controlled studies are lacking.[4,12,13]

The treatment landscape for severe AD is changing rapidly, with several new systemics already approved for patients aged ≥6 years. Encompassing biologics and small molecules, these new agents target various inflammatory pathways and include anti-interleukin (IL) monoclonal antibodies and oral Janus

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kinase (JAK) inhibitors.[14] Dupilumab, an anti-IL-4 receptor-α monoclonal antibody that blocks IL-4 and IL-13 signalling, was the first approved biologic for AD.[15] First licensed in adults in Europe in 2017, it is now also approved for children aged ≥6 years with moderate-to-severe AD.[16]

Soon, more systemic agents will become available in Europe for the treatment of moderate-to-severe AD in adolescents and possibly also in children. The advent of these treatments has sparked discussion on the use of systemics for moderate-to-severe childhood AD, prompting questions around clinical decision-making.[17] Comprehensive, consensus-based European position papers and guidelines exist for managing AD in adults and children;[9–11] however, practical guidance for using systemic and biologic therapies specifically in children is limited, often because supporting evidence is lacking.

This project convened dermatologists, paediatricians and paediatric allergists from Northern Europe to develop practical consensus recommendations for paediatric AD. These statements supplement, not replace, the recommendations in international and regional guidelines, including those published by the European Academy of Allergy and Clinical Immunology (EAACI),[18] the European Task Force on Atopic Dermatitis/European Academy of Dermatology and Venereology (ETFAD/EADV)[9] and the European Dermatology Forum (EDF).[10,11] They are intended to help clinicians make treatment decisions within this evolving landscape. This project assumes topical therapy has been optimized and maintained.[19] Discussion of topical treatments is outside scope: Readers are referred instead to the ETFAD/EADV and EDF guidelines.[9–11,20]

Methods

Delphi process: overview

This project used the Delphi method to reach consensus on how to best manage children aged ≥2 years with severe AD in need of systemic therapies. Infants aged <2 years were not considered, owing to the extremely limited experience of treating such severe disease with systemic treatment in this age group.

The Delphi process is widely used for reaching consensus between experts in a given field, particularly when expert opinion is important in shaping judgements.[17,21–23] Delphi involves a predefined number of rounds of questioning, usually in a structured format, with anonymous answers given then shared among participants between rounds. This allows participants to alter their responses based on their peers' opinions and promotes the convergence of opinion.

Participants' roles

Our expert group comprised 19 experts in paediatric AD the clinical management. All were dermatologists except one paediatrician and one paediatric allergist. The experts were selected for their expertise, publishing records, national and regional standing and interest in the topic. The group was directed by a subset of experts – a steering committee – who guided the project scope, objectives and focus; advised on key topics and questions arising from the Delphi process; and guided the iteration of the statements between rounds. At least two representatives from each country were included.

The chairing of meetings, data analysis and project management was done by an impartial Delphi facilitator, assisted by a medical writer. The sponsor did not participate in discussions and had no input on the questionnaire, Delphi conduct or the consensus. The views and opinions reported in this manuscript are those of the authors.

Questionnaire development

The steering committee met virtually in March 2021 to discuss project scope. This included discussion of which children to consider, which clinicians to address and the key considerations in AD management not covered by existing guidelines.

A comprehensive gap analysis of guidelines[9–11] was done to identify areas where best practices are unclear: This project focused on these areas. Based on these findings, draft statements were developed, refined and agreed by the steering committee. Round 1 was put to the full expert group as an online survey, with the option to record additional free-text responses.

The steering committee met virtually again in May 2021 to review the Round 1 responses and to adjust those statements achieving no or partial consensus, according to the respondents' feedback. The revised Round 2 survey was put to the full expert group, and all experts discussed the final responses and developed the final consensus recommendations.

Definitions of consensus

Responses were recorded using a 9-point Likert scale, from 1 ('Strongly disagree') to 9 ('Strongly agree'). Consensus to a statement was defined *a priori* by the steering committee if 75% of responses scored 7, 8 or 9 ('Agree' to 'Strongly agree'), in an approach similar to other consensus projects.[24–28] Partial consensus occurred if some – but not all – parts of a multipart question reached consensus.

Expert meeting

The full expert group met virtually in June 2021. The agenda of the meeting was designed by the steering committee. The results from Rounds 1 and 2 were summarized, and statements with no consensus were discussed in small breakout groups, with the aim of clarifying the experts' reasons for non-consensus. The experts gave reasons and context to their opinions and explained why they did (or did not) reach consensus; no further consensus voting was undertaken.

Results

An overview of the Delphi method and key results is shown in Fig. 1.

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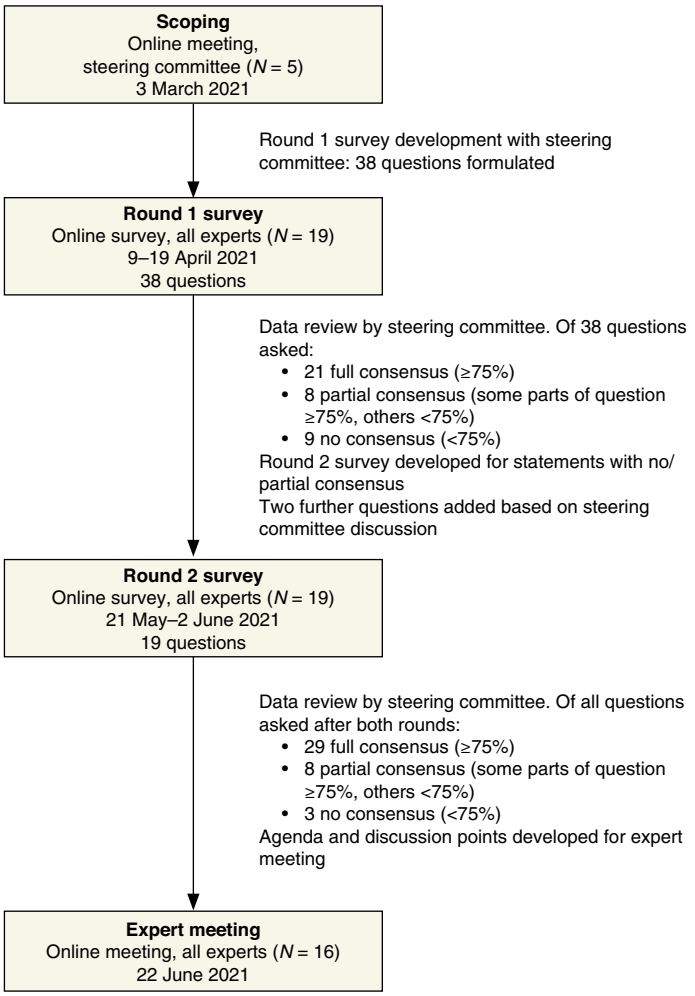

Figure 1 An overview of the Delphi method used in this consensus project.

Thirty-eight statements were put to the experts in Round 1, and all responded to all statements. After Round 1, the comments and responses not reaching full consensus were discussed by the steering committee to create the Round 2 survey. Statements that reached full consensus in Round 1 were not asked again. Statements on specific agents were amended to allow the answer, 'No opinion or experience', to ensure the recommendations are based on the opinions of only physicians with experience using a particular therapy.

One free-text box was added to invite the experts to provide other advice or comments. Two new questions relating to the suitability of systemic treatments alongside vaccinations were added.

Nineteen new or amended statements were put to the experts after these revisions (Round 2). The statements reaching consensus, partial consensus or no consensus after both Delphi rounds are shown in Tables 1–9.

General principles for using systemic therapies in children

Using many validated tools is encouraged in daily practice, but the Dermatology Family Index was considered unfeasible (Table 1).

Therapeutic patient education is valuable for managing symptoms and signs (Table 2).

A diagnosis of severe AD *and* persistent disease uncontrolled after optimizing non-systemic treatments and adherence is enough to consider systemic therapy (Table 3).

Long-term control should reduce objective signs of disease, meet the patient's goals and alleviate symptoms of particular concern (Table 4).

Treatment choice should consider comorbidities, medical history and other medications (Table 5).

Cyclosporin A is considered a suitable short-term treatment across all age groups (Table 6).

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Table 1 Assessing the severity and burden of childhood AD

	Statement	Status	Likert score %†			Mean score
			1–3	4–6	7–9	
1	A comprehensive evaluation of the psychological, social and behavioural impact of AD, including school/work absenteeism, on the patient and family is recommended	Consensus (Round 1)	0	5	95	8.3
2	A comprehensive evaluation of the burden of AD on the family is recommended	Consensus (Round 1)	0	16	84	7.7
3	The impact of a child's AD on the quality of life of the patient and the wider family should be thoroughly evaluated	Consensus (Round 1)	0	5	95	8.2
4	The use of validated tools such as SCORAD, EASI or POEM to assess disease severity and symptom burden and to monitor treatment success is encouraged	Consensus (Round 1)	0	11	89	8.0
5	The use of validated tools to monitor the fluctuation of AD severity over time, e.g., POSCORAD or POEM, is important in assessing the burden of disease	Consensus (Round 1)	5	16	79	7.2
6	The use of tools such as CDLQI to fully assess the patient's QoL is encouraged	Consensus (Round 1)	5	11	84	7.3
7	The use of tools such as the Dermatology Family Index (DFI) to fully assess the family's QoL is encouraged	No consensus	11	42	47	5.9

Rows highlighted in green highlight statements that reached consensus; rows in red are those with no consensus.
AD, atopic dermatitis; CDLQI, Children's Dermatology Life Quality Index; DFI, Dermatology Family Index; EASI, Eczema Area and Severity Index; POEM, Patient-oriented Eczema Measure; (PO-)SCORAD, (Patient-oriented) Scoring Atopic Dermatitis; QoL, quality of life.
†All experts (N = 19) responded to all statements.

Table 2 Therapeutic patient education ('eczema school')

	Statement	Status	Likert score %†			Mean score
			1–3	4–6	7–9	
8	Therapeutic patient education is valuable in helping patients and caregivers manage AD symptoms and signs	Consensus (Round 1)	0	0	100	8.6
9	Therapeutic patient education is important in improving the QoL of patients and their families	Consensus (Round 1)	0	11	89	8.0
10	Therapeutic patient education should include a focus on promoting effective adherence to therapies and the avoidance of factors aggravating AD	Consensus (Round 1)	0	5	95	8.5
11	Patient and/or caregiver hesitancy or phobia around the use of specific therapies (both topical and systemic) should be explored and addressed	Consensus (Round 1)	0	0	100	8.7

Rows highlighted in green highlight statements that reached consensus; rows in red are those with no consensus.
AD, atopic dermatitis.
†All experts (N = 19) responded to all statements.

Dupilumab and methotrexate are suitable for long-term use in children aged 6–17 years; there was no consensus on long-term treatment suitable for children aged 2–6 years (Table 7).

Oral glucocorticosteroids should be avoided in all age groups: Targeted treatments are preferable (Table 8).

The experts align with the EADV's position on vaccinations and systemic treatments (Table 9).

Discussion

Assessing the severity and burden of childhood AD

Existing guidelines include algorithms and narrative to help physicians choose treatments for children and adolescents, based on AD severity.[9,11] The experts agreed that validated tools such as Scoring Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), *etc.*, are useful for assessing disease severity, symptom burden and quality of life and for monitoring treatment success: Their use is encouraged in daily practice. Conversely, the experts agreed that using the Dermatology Family Index is unfeasible in daily practice.

Therapeutic patient education ('eczema school')

Concerns over side effects, for example, 'corticophobia' (concern about TCS), are often held by physicians, patients and families. These fears can reduce treatment adherence, and mean physicians may hesitate to prescribe systemic AD therapies.[17,29–31] The question of how to reduce these concerns remains unanswered: While some studies suggest that targeted patient education ('eczema schools') may mitigate such concerns,[32,33] others conclude that even when patients are armed with more knowledge, their fear levels remain unchanged.[34,35] This expert group reached 100% consensus that therapeutic patient education is valuable and agreed that hesitancy and phobia need to be specifically addressed.

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Table 3 Which children are candidates for systemic therapy?

	Statement	Status	Likert score %†,‡			Mean score
			1–3	4–6	7–9	
12	All children aged 2 years and over are candidates for systemic therapy when they meet the following severity threshold:					
	(a) they have a clear clinical diagnosis of severe AD	Consensus (Round 2)	11	11	79	6.8
	(b) they have persistent disease that is uncontrolled even after optimizing non-systemic treatments and treatment adherence	Consensus (Round 1)	0	5	95	8.0
13	Children aged 2 years and over with moderate AD, comorbidities and a highly impaired QoL may also be candidates for systemic treatment	Consensus (Round 1)	0	5	95	7.8

Rows highlighted in green highlight statements that reached consensus; rows in red are those with no consensus.
AD, atopic dermatitis; QoL, quality of life.
†All experts (N = 19) responded to all statements.
‡Sum of percentages does not always add up to 100% due to discrepancies in rounding to whole numbers.

Table 4 Principles of systemic therapy use in children aged ≥2 years

	Statement	Status	Likert score %†,‡			Mean score
			1–3	4–6	7–9	
14	The goal of treatment with systemic therapy is to achieve long-term disease control while minimizing the risk of treatment toxicity	Consensus (Round 1)	0	5	95	8.6
15	Long-term disease control includes:					
	(a) reducing disease activity	Consensus (Round 1)	0	0	100	8.6
	(b) reducing symptoms of concern to the patient and family	Consensus (Round 1)	5	0	95	7.8
	(c) reducing the frequency and severity of AD flares	Consensus (Round 1)	0	0	100	8.5
	(d) reducing reliance on rescue or 'on demand' medication to treat flares	Consensus (Round 2)	0	16	84	7.5
	(e) reducing the use of non-systemic anti-inflammatory maintenance medication	No consensus	0	26	74	7.1
	(f) increasing QoL	Consensus (Round 1)	0	0	100	8.4
16	Systemic therapies should be used in combination with emollients	Consensus (Round 1)	5	5	89	7.8
17	Systemic therapies may be combined with topical anti-inflammatory treatments if the combination is not contraindicated	Consensus (Round 1)	0	5	95	8.3
18	Systemic therapy should be considered when the severity threshold is met and one or more of the following applies:					
	(a) the patient experiences frequent moderate-to-severe AD flares despite optimization of a non-systemic anti-inflammatory maintenance regimen	Consensus (Round 1)	0	0	100	8.5
	(b) the patient experiences continuous AD symptoms, for example, itch, despite optimization of a non-systemic anti-inflammatory maintenance regimen	Consensus (Round 1)	0	5	95	7.9
	(c) the patient experiences severe side effects from non-systemic anti-inflammatory maintenance treatment	Consensus (Round 1)	0	11	89	7.7
	(d) excessive use of non-systemic anti-inflammatory maintenance treatment is causing objective side effects	Consensus (Round 1)	0	11	89	8.3
	(e) the patient's and family's QoL is significantly impaired despite the current non-systemic anti-inflammatory maintenance regimen	Consensus (Round 1)	0	11	89	7.7

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Table 4 *Continued*

	Statement	Status	Likert score %†,‡			Mean score
			1–3	4–6	7–9	
19	Before initiating systemic therapy, the patient should have failed to achieve disease control with:					
	(a) 1–4 weeks of medium-to-high potency topical anti-inflammatory treatment daily, followed by an appropriate usage period of proactive, compliant maintenance therapy	Consensus (Round 1)	0	5	95	8.0
	(b) Wet wrap therapy	No consensus	47	32	21	3.8
20	Early intervention with systemic therapy should be considered for children aged 2 years and above who meet the severity threshold for systemic treatment and have risk factors for persistent atopic disease, such as early onset AD, polysensitization and a family history of atopy	No consensus	5	26	68	6.8
21	Treatment targets to be reached after the first 3 and 6 months of systemic therapy should be agreed as part of shared decision-making between the clinician, patient and family	Consensus (Round 1)	5	11	84	7.3
22	Both patient QoL and (to a lesser extent) family QoL should be key considerations driving shared decision-making on treatment regimens	Consensus (Round 2)	5	0	95	7.5
23	To treat an AD flare occurring during topical anti-inflammatory treatment, it is appropriate to restart systemic treatment with a previously effective and well-tolerated systemic regimen	Consensus (Round 1)	0	11	89	7.4
24	The potential long-term toxicity of repeat dosing with systemics should be carefully considered	Consensus (Round 1)	0	0	100	8.4
25	Stopping or switching to an alternative systemic therapy is appropriate if loss of disease control is observed, if bothersome patient symptoms are unresolved or if the systemic treatment is poorly tolerated	Consensus (Round 1)	0	0	100	8.4
26	When switching from one systemic treatment to another, it is not necessary to meet the severity threshold for systemic treatment again	Consensus (Round 1)	0	5	95	7.8

Rows highlighted in green highlight statements that reached consensus; rows in red are those with no consensus.
†All experts (N = 19) responded to all statements.
‡Sum of percentages does not always add up to 100% due to discrepancies in rounding to whole numbers. AD, atopic dermatitis; QoL, quality of life.

The EDF consensus-based guidelines advise that systemic therapies – including cyclosporine A, methotrexate, azathioprine, dupilumab or mycophenolate mofetil – may be considered only for children with severe (SCORAD >50) or persistent AD.[9] However, in practice, deciding when and how to escalate to systemic treatment – and for whom – is less straightforward.[17] Clinicians must recognize which children need systemic treatment; assess the risk/benefit ratio of available treatments; decide which agent to use, for which ages and for how long; and then monitor treatment response. Such decisions must be individualized; thus, guidelines are of only partial use. Notably, the practicalities on prescribing systemic therapies vary among countries: In some, this can be done directly from secondary care; in others, this necessitates tertiary care referral.

Which children are candidates for systemic therapy?

Treating children aged <2 years was out of scope for this project. Children <2 years needing systemic AD treatment are extremely rare, and even among our experts, direct experience is limited. Furthermore, age <2 years is the cutoff for AD trials and so empirical evidence is non-existent. The experts suggest that treating such children would involve such a tailored approach that broad recommendations would not be appropriate.

All children aged ≥2 years are potential candidates for systemic therapy if they have a clear clinical diagnosis of severe AD *and* persistent disease uncontrolled after optimizing non-systemic treatments and adherence. As part of this optimization, the experts suggest trialling 1–4 weeks of intensive, medium-to-high

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Table 5 Use of specific systemic therapies in children

	Statement	Status	Likert score %†,‡			Mean score
			1–3	4–6	7–9	
27	The selection of systemic therapy should take into account:					
	(a) patient disease history and (to a lesser extent) family disease history	No consensus	11	16	74	6.7
	(b) comorbidities	Consensus (Round 1)	0	5	95	8.0
	(c) prior responses to treatment	Consensus (Round 1)	0	0	100	8.2
	(d) patient and family preference	Consensus (Round 1)	0	11	89	7.4
	(e) price of treatment	No consensus	11	26	63	6.4
	(f) risk/benefit ratio of treatment	Consensus (Round 1)	0	0	100	8.4
	(g) route of administration (e.g. pills, injections)	No consensus	5	37	58	6.6
28	Clinicians should refer to their local, national or international guidelines to guide specific dosing and treatment escalation.	Consensus (Round 2)	5	5	89	7.8

Rows highlighted in green highlight statements that reached consensus; rows in red are those with no consensus.
†All experts (N = 19) responded to all statements.
‡Sum of percentages does not always add up to 100% due to discrepancies in rounding to whole numbers.

Table 6 Use of specific short-term systemic therapies

In your opinion, systemic treatments suitable for short-term use (up to 8 weeks) in children include (in alphabetical order):	Q29: aged 2–6 years				Q30: aged 6–12 years				Q31: aged 12–17 years			
	Likert score, %§,¶			Mean score	Likert score, %§,¶			Mean score	Likert score, %§,¶			Mean score
	1–3	4–6	7–9		1–3	4–6	7–9		1–3	4–6	7–9	
(a) Azathioprine†	82	6	12	3.0	76	12	12	3.2	76	18	6	2.9
	n = 17				n = 17				n = 17			
(b) Cyclosporin A†	0	16	84	7.7	0	11	89	7.8	0	11	89	7.7
	Consensus n = 19				Consensus n = 19				Consensus n = 19			
(c) Dupilumab‡	37	42	21	4.4	32	37	32	5.0	32	37	32	5.0
	n = 19				n = 19				n = 19			
(d) Methotrexate†	56	22	22	3.8	56	28	17	3.9	56	33	11	3.6
	n = 18				n = 18				n = 18			
(e) Mycophenolate mofetil†	71	24	6	3.1	71	24	6	3.2	71	29	0	2.8
	n = 17				n = 17				n = 17			

Rows highlighted in green highlight statements that reached consensus; rows in red are those with no consensus.
†Indicates off-label therapy.
‡Indicates off-label therapy in children aged 2–6 years.
§N numbers relate to the number of experts (N = 19) who responded to each statement. 'No opinion or experience' responses were excluded from percentage and mean calculations.
¶Sum of percentages does not always add up to 100% due to discrepancies in rounding to whole numbers.

potency topical anti-inflammatory treatment daily, followed by an appropriate usage period of proactive, compliant maintenance therapy: an approach advocated by European experts.[17]

Principles of systemic therapy use in children aged ≥2 years

The decision to escalate to systemic therapy should be based not only on clinical presentation and objective severity scores, but also on a thorough understanding of quality of life impairment: In some cases, apparently moderate AD can substantially impair a child's or family's quality of life and warrant systemic treatment.[17] Therefore, holistic and comprehensive evaluation of the psychological, social and behavioural impact of AD, including on school and work absenteeism, is vital to understand the extent of morbidity. Indeed, this has been highlighted by previous expert groups and researchers.[17,36,37]

Good long-term disease control should reduce objective signs of disease, e.g., frequency and severity of flares, and meet the

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Table 7 Use of specific long-term systemic therapies

In your opinion, systemic treatments suitable for long-term use (8 weeks or longer) in children include (in alphabetical order):	Q32: aged 2–6 years				Q33: aged 6–12 years				Q34: aged 12–17 years			
	Likert score, %§,¶			Mean score	Likert score, %§,¶			Mean score	Likert score, %§,¶			Mean score
	1–3	4–6	7–9		1–3	4–6	7–9		1–3	4–6	7–9	
(a) Azathioprine†	53	18	29	3.9	41	29	29	4.2	41	18	41	4.7
		n = 17				*n* = 17				*n* = 17		
(b) Cyclosporin A†	16	32	53	6.0	11	21	68	6.3	11	21	68	6.3
		n = 19				*n* = 19				*n* = 19		
(c) Dupilumab‡	5	37	58	7.0	0	5	95	8.3	0	5	95	8.4
		n = 19				Consensus *n* = 19				Consensus *n* = 19		
(d) Methotrexate†	17	17	67	6.6	6	11	83	7.2	6	17	78	7.4
		n = 18				Consensus *n* = 18				Consensus *n* = 18		
(e) Mycophenolate mofetil†	50	19	31	4.2	38	38	25	4.6	38	38	25	4.8
		n = 16				*n* = 16				*n* = 16		

Rows highlighted in green highlight statements that reached consensus; rows in red are those with no consensus.
†Indicates off-label therapy.
‡Indicates off-label therapy in children aged 2–6 years.
§*N* numbers relate to the number of experts (*N* = 19) who responded to each statement. 'No opinion or experience' responses were excluded from percentage and mean calculations.
¶Sum of percentages does not always add up to 100% due to discrepancies in rounding to whole numbers.

Table 8 Other considerations related to systemic treatment selection

	Statement	Status	Likert score %‡,§			Mean score
			1–3	4–6	7–9	
35	Oral glucocorticosteroids should generally be avoided for short-term (up to 8 weeks) treatment of flares in children aged:					
	(a) 2–6 years	Consensus (Round 2)	5	5	89	7.5
	(b) 6–12 years	Consensus (Round 2)	5	5	89	7.4
	(c) 12–17 years	Consensus (Round 2)	5	16	79	7.2
36	Oral glucocorticosteroids are unsuitable for long-term use (8 weeks or longer) as maintenance therapy in children in children aged:					
	(a) 2–6 years	Consensus (Round 2)	11	0	89	8.0
	(b) 6–12 years	Consensus (Round 2)	11	0	89	8.0
	(c) 12–17 years	Consensus (Round 2)	11	0	89	8.0
37	Targeted biological therapies are preferable to therapies causing broader immunosuppression in children	Consensus (Round 1)	0	16	84	7.8
38	Notwithstanding your country's local guidelines and reimbursement requirements, in your opinion, conventional systemic therapy (such as methotrexate,† cyclosporine) need NOT necessarily be used before initiating new systemic therapies (such as biologics) in children	Consensus (Round 2)	0	11	89	7.8

Rows highlighted in green highlight statements that reached consensus; rows in red are those with no consensus.
†Indicates off-label therapy.
‡All experts (*N* = 19) responded to all statements unless otherwise indicated.
§Sum of percentages does not always add up to 100% due to discrepancies in rounding to whole numbers.

patient's goals and alleviate symptoms of particular concern to them and their family. For example, reducing itch, restoring sleep and reducing reliance on rescue medication were among the needs heard most frequently in the experts' practice, mirror what is reported by focus groups of caregivers for children with AD.[38]

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Table 9 Considerations for vaccination schedules and systemic treatment

	Statement	Status	Likert score, %†			Mean score
			1–3	4–6	7–9	
39	When prescribing systemic medications to treat AD, it is important to be aware of the vaccination status and plans of the patient‡	Consensus (Round 2)	0	0	100	8.2
40	The selection of systemic medication in children receiving vaccinations should take into account‡:					
	(a) the mode of action of the systemic medication and its likely impact on vaccine response	Consensus (Round 2)	0	16	84	7.5
	(b) the type of vaccine (e.g. live or non-live)	Consensus (Round 2)	0	11	89	8.2

Rows highlighted in green highlight statements that reached consensus.
†All experts (N = 19) responded to all statements.
‡Questions 39 and 40 were not asked in Round 1 of the survey; these were added based on free-text comments following the review of Round 1.
AD, atopic dermatitis.

To maximize adherence and the likelihood of treatment success, treatment considerations for children must include the patient's personal goals, individual concerns and route of administration. For injectable drugs, injection-site reactions and caregivers' competence and willingness to administer must be considered, as should palatability for oral drugs.

The experts stress that we must recognize the seriousness of childhood AD and reduce the temptation to under-treat, particularly younger patients.[39] Not only may undertreatment mean patients and families continue struggling with symptoms, it increases the likelihood of long-term psychological sequelae.[40,41] The experts did not fully agree that the presence of risk factors for persistent atopic disease *per se* necessitates early systemic therapy, particularly in the youngest children, primarily due to concerns regarding side effects and lack of evidence for long-term efficacy at halting the atopic march.

Which drugs for long- and short-term use?

The question 'how long' to treat children with systemics – and with which agents – was a key focus of discussions. Experts broadly agreed that 'short-term' treatment means <8 weeks and 'long-term' ≥8 weeks, but this is flexible and depends on individuals' needs and responses. All agreed that systemic treatment should reduce the reliance on repeated short-term interventions and rescue medications. Indeed, overuse of potent TCS represents an indication for systemic therapy. Additionally, the experts agreed that treatment choice should consider patient comorbidities, medical history and other medications.

A key discussion theme has been the difficulties in treating young children (aged 2–6 years) with systemics for moderate-to-severe AD. In accordance with EADV guidelines and the opinions of other expert groups,[9] the experts recommend short-term use of cyclosporine A in all ages, because of its rapid onset of action favourable tolerability and effectiveness.[11,42,43] However, the experts could not reach consensus regarding the best systemic agents to use for long-term treatment in the youngest age group. Existing guidelines are also largely silent on this topic, primarily due to extremely limited real-world experience. Azathioprine is to be avoided in children of any age – in short- or long-term treatment – because of its unfavourable safety profile. ETFAD guidelines suggest azathioprine could be an option for severe or persistent AD, but recognize that good evidence in children is lacking.[9,11] Likewise, adverse safety concerns promoted consensus that oral glucocorticosteroids are unsuitable in all but exceptional short-term circumstances, and never for long-term use: a position mirrored by the EADV and other European consensus groups.[11,44–46] Similarly, neither mycophenolate mofetil nor methotrexate was favoured for short-term use, because their slow onset of action means treatment for <3 months is unlikely to yield clinical benefit. Some experts expressed concern over gastrointestinal side effects with mycophenolate mofetil[47] and hepatotoxicity with methotrexate,[48,49] which may influence the suitability of these agents for some children. The experts agreed targeted therapies are preferable to those causing broader immunosuppression. However, they cautioned that more trial and real-world data are needed before recommending this for the youngest age group.

Most experts agreed methotrexate is favourable for long-term treatment of children aged 6–12 and 12–17 years, and some agreed with its use also in children aged 2–6 years. Many agreed dupilumab seems promising for children of all ages; however, the lack of published data on its use in the youngest children (2–6 years) and its lack of approval and reimbursement in some countries precludes firm recommendation for its use at this time.

The mode of action of any systemic treatment and its likely impact on vaccine response must be considered, particularly for live-attenuated vaccines and immunosuppressive therapy, as has been recently reviewed in detail.[50] The experts align fully with the position of the EADV: No evidence exists that routine childhood vaccinations impact AD development and that, except during acute flares or during cyclosporine A therapy, children with AD should be vaccinated according to their national vaccination plan.[10]

Future avenues

Studies are ongoing with several biologics and small molecules targeting different inflammatory pathways in AD, which will expand the treatments for paediatric AD. Most promising are oral JAK inhibitors and anti-IL-13 and anti-IL-31 antibodies. Several trials are ongoing in adolescents and children with AD. Among them are Phase 3 trials of tralokinumab and

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lebrikizumab (both anti-IL-13) in adolescents aged 12–17 years.[51–54] For children aged ≥2 years, two Phase 3 trials with baricitinib (JAK1/2 inhibitor) are underway[55,56] and a Phase 1 study with upadacitinib (JAK1 inhibitor) is recruiting for children as young as 6 months.[57] A further study with dupilumab recently reported favourable efficacy in children as young as 6 months.[58] Other studies aiming to evlauate nemolizumab (anti-IL-31) in children aged ≥12 years are recruiting.[59,60]

Limitations

The authors note some limitations to this consensus. Firstly, this initiative involved childhood AD specialists, many of whom practise in secondary or tertiary care settings. While these experts are well positioned to make recommendations based on their extensive practice and experience, their perspective means their consensus may not directly address the challenges for dermatologists working privately or in general dermatology clinics. Secondly, no patients or caregivers were consulted, arguably reducing its applicability to patients' lives. However, we suggest that since our consensus aligns closely with first-hand accounts from patients and caregivers,[38,61–63] and with more widely influenced international guidelines,[9,10,18] our recommendations are both relevant and sensitive to patient and caregiver concerns. Notwithstanding these potential drawbacks, a strength of this consensus is its focus on several geographically similar, related, yet diverse European countries whose healthcare systems, local preferences and reimbursement structures differ significantly.

Conclusions

This Northern European consensus clarifies how best to treat children needing systemic treatment for moderate-to-severe AD and supplements existing guidelines. The experts recommend all children aged ≥2 years are candidates for systemic therapy if they have a clear diagnosis of severe AD *and* persistent disease uncontrolled after optimizing non-systemic treatments and adherence. Systemic treatment should achieve long-term disease control and reduce the reliance on short-term interventions and rescue medications. For short-term use, cyclosporine A is recommended for all age groups, and for long-term use, methotrexate and dupilumab are recommended for children aged ≥6 years. The experts could not reach full consensus regarding the best long-term systemics for the youngest age group, although methotrexate and dupilumab were favoured.

Recent approvals of new therapies and an active research pipeline with other biologics and small molecules mean that the future is looking brighter for children and families struggling with severe AD. We hope this advancing field of medicine will offer new means to improve their quality of life in future.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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