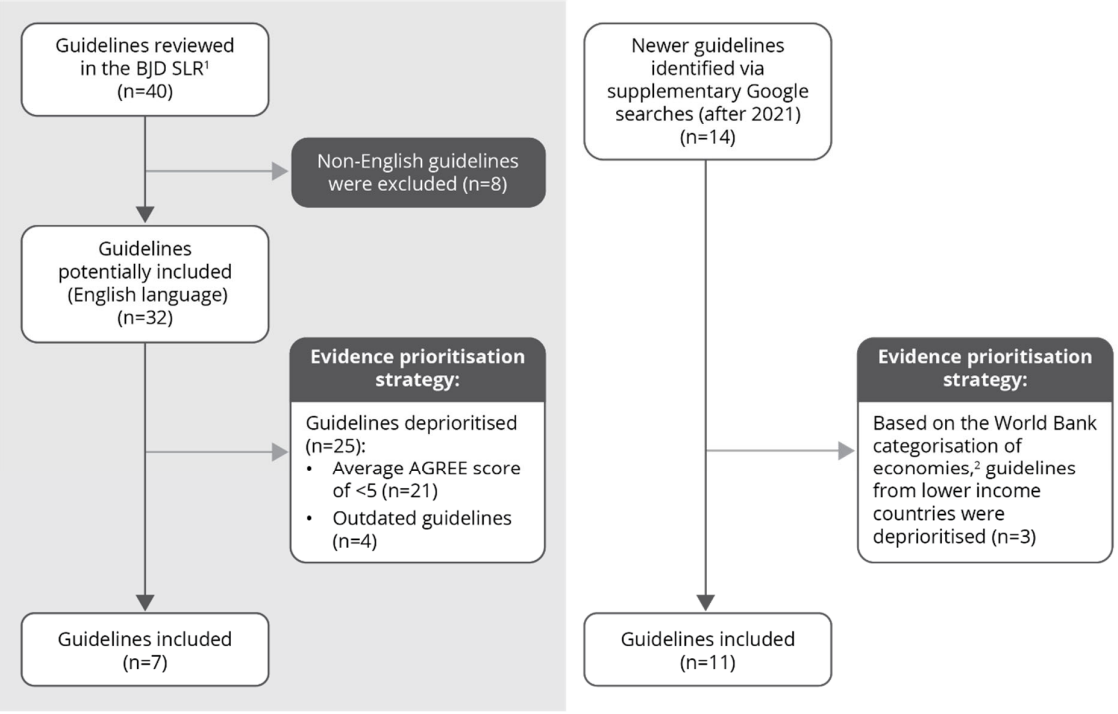
Supplementary materials to: Yew YW, Alagappan U, Aw D, et al. Updated consensus guidelines for management of moderate-to-severe atopic dermatitis in Singapore: Integrating biologics, Janus kinase inhibitors and conventional therapies. DOI: https://doi.org/10.47102/annals-acadmedsg.2024158

Supplementary materials

Supplementary Fig. S1. 18 guidelines reviewed.



Supplementary Table S1. Evolution of Delphi statements between rounds.

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
Disease Assessment				
1	An assessment of AD disease severity should be performed. This assessment should encompass objective clinical signs, as well as the severity of symptoms and the impact of AD on the patient's quality of life.	✓ **Consensus reached** • **83% Strongly Agree** • **17% Agree**		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
2	In addition to a dermatological examination, outcome measures such as SCORing Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), Dermatology Life Quality Index (DLQI), Itch Numeric Rating Scale (NRS) and the Patient Oriented Eczema Measure (POEM) complement the assessment and are useful for monitoring disease activity and impact, as well as to guide overall therapy.	✓ **Consensus reached** • **42% Strongly Agree** • **58% Agree**		
Treatment Goals				

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
3	The goal of AD treatment is to establish disease control, minimise symptoms and reduce impact on patients' quality of life.	✓ **Consensus reached** • **92% Strongly Agree** • 8% Disagree		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
4	Useful initial targets to measure treatment response among moderate-to-severe AD patients include achieving a 50% reduction of SCORAD points (SCORAD-50), achieving a 50% reduction of EASI points (EASI-50), a reduction of DLQI by at least 4 points, a reduction of NRS by at least 3 points or a reduction of POEM by at least 4 points within 3 months of treatment initiation.	✓ **Consensus reached** • **83% Agree** • 17% Neutral		
Treatment Approach				

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
5	A collaborative approach involving shared decision-making among patients, caregivers and healthcare providers is essential. Discussions should involve treatment goals, expectations, treatment plans, treatment options, potential adverse effects and the preferences of the patients and caregivers.	✓ **Consensus reached** • **92% Strongly Agree** • **8% Agree**		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
6	The decision to initiate systemic therapies (conventional and novel [including biologics and small molecules]) for moderate-to-severe AD should be made by dermatologists, due to the potential for misdiagnoses (e.g. cutaneous T cell lymphoma) and adverse reactions.	✓ **Consensus reached** • **75% Strongly Agree** • **17% Agree** • 8% Neutral		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
Conventional Treatments: Treatment Paradigm for Moderate-to-Severe AD				
7	For moderate-to-severe AD, emollients remain the mainstay of general disease management.	✓ **Consensus reached** • **67% Strongly Agree** • **17% Agree** • 16% Disagree		
8	Topical corticosteroids are used as first-line therapy to treat acute exacerbations and maintain AD control in non-sensitive areas (e.g. hands and feet).	✓ **Consensus reached** • **75% Strongly Agree** • **17% Agree** • 8% Neutral		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
9	Topical calcineurin inhibitors should be used as first-line therapy for sensitive areas (e.g. neck, eyelids and genital areas), where topical corticosteroid use is likely to be associated with adverse events.	✗ **<u>Consensus not reached; statement reformulated</u>** • **33% Strongly Agree** • **17% Agree** • 33% Neutral • 17% Disagree 	The use of topical calcineurin inhibitors should be considered, particularly for sensitive areas (e.g. neck, eyelids and genital areas) where topical corticosteroid use is likely to be associated with adverse events.	✓ **<u>Consensus reached</u>** • **58% Strongly Agree** • **42% Agree**

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
10		**New statement formulated**	The use of topical phosphodiesterase-4 inhibitors (e.g. crisaborole) should be considered, particularly for sensitive areas (e.g. neck, eyelids, and genital areas) where topical corticosteroid use is likely to be associated with adverse effects.	✓ **Consensus reached** • **50% Strongly Agree** • **50% Agree**

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
11	For the control of chronic moderate-to-severe AD, phototherapy should be considered before using any systemic anti-inflammatory agents.	✗ **<u>Consensus not reached; statement reformulated</u>** • **17% Strongly Agree** • **17% Agree** • 17% Neutral • 41% Disagree • 8% Strongly Disagree 	For the control of chronic moderate-to-severe AD, phototherapy could be considered as an alternative before using any systemic anti-inflammatory agents.	✓ **<u>Consensus reached</u>** • **17% Strongly Agree** • **75% Agree** • 8% Neutral

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
X	Phototherapy should be discontinued upon initiation of traditional systemic anti-inflammatory agents (e.g. ciclosporin) to avoid the risk of co-carcinogenicity.	✗ **<u>Consensus not reached; statement reformulated</u>** • **25% Strongly Agree** • **17% Agree** • 50% Neutral • 8% Disagree	Phototherapy should be used with caution when used in combination with systemic anti-inflammatory agents to avoid the risk of co-carcinogenicity.	✗ **<u>Consensus not reached</u>** • **25% Strongly Agree** • **50% Agree** • 17% Neutral • 8% Disagree

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
12	In cases of persistent moderate-to-severe AD, a holistic assessment is needed to decide when to initiate systemic therapy. This assessment should consider disease severity, quality of life, patient factors (e.g. adherence, avoidance of irritants and optimisation of treatment), alternative diagnoses and whether intensive topical treatment and phototherapy have been trialled.	✓ **Consensus reached** • **83% Strongly Agree** • **17% Agree**		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
13	Among conventional systemic anti-inflammatory agents, ciclosporin is the recommended first-line treatment option, with methotrexate or azathioprine as secondary options.	✗ **Consensus not reached; statement reformulated** • **25% Strongly Agree** • **25% Agree** • 33% Neutral • 17% Disagree	Among conventional systemic anti-inflammatory agents, ciclosporin has the best evidence in the treatment of moderate-to-severe AD.	✓ **Consensus reached** • **8% Strongly Agree** • **92% Agree**

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
14	Systemic corticosteroids should be considered only as rescue therapy for acute flares, and not for long-term use in chronic AD.	✓ **Consensus reached** • **83% Strongly Agree** • **17% Agree**		
15		**New statement formulated**	Long-term high-potency topical corticosteroid use for moderate-to-severe AD is not recommended.	✓ **Consensus reached** • **17% Strongly Agree** • **67% Agree** • 16% Disagree

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
16		**New statement formulated**	Wet-wrap therapy in combination with high-potency topical corticosteroids should be used with caution to minimise potential adverse events.	✓ **Consensus reached** • **42% Strongly Agree** • **58% Agree**
Conventional Treatments: Steroid Tapering and Phobia)				
17	Topical corticosteroids are an effective treatment for moderate-to-severe AD. Tapering of corticosteroids should be initiated on adequate control of disease.	✓ **Consensus reached** • **50% Strongly Agree** • **42% Agree** • 8% Neutral		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
18	Tapering strategies involve using less potent corticosteroids or maintaining a potent corticosteroid while reducing application frequency. All dose tapering should be gradual to avoid withdrawal rebound.	✗ **<u>Consensus not reached; statement reformulated</u>** • **50% Strongly Agree** • **17% Agree** • 25% Neutral • 8% Disagree	Tapering strategies can include using less potent corticosteroids, reducing application frequency of potent corticosteroids or using topical corticosteroids in combination with topical calcineurin inhibitors or phosphodiesterase-4 inhibitors.	✓ **<u>Consensus reached</u>** • **33% Strongly Agree** • **59% Agree** • 8% Neutral

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
19	There is a need to address steroid phobia to improve adherence to topical corticosteroids in the management of AD. At treatment initiation and follow-ups, healthcare providers should screen for steroid phobia (e.g. using the Topical Corticosteroid Phobia [TOPICOP] scale) and individualise patient education if patients express concerns about steroid use.	✓ **Consensus reached** • **33% Strongly Agree** • **59% Agree** • 8% Disagree		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
Novel Treatments (Biologic – Treatment Selection [Dupilumab-Specific Recommendations])				
20	Dupilumab can be considered for first-line systemic treatment in patients with moderate-to-severe AD.	✗ **Consensus not reached; statement reformulated** • **33% Strongly Agree** • **42% Agree** • 17% Neutral • 8% Disagree	Dupilumab could be considered for first-line systemic treatment in patients with moderate-to-severe AD.	✓ **Consensus reached** • **42% Strongly Agree** • **50% Agree** • 8% Disagree

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
21	Dupilumab is recommended as the first-line systemic treatment for patients with both moderate-to-severe AD and concomitant type 2 allergic disease.	✓ **Consensus reached** • **25% Strongly Agree** • **59% Agree** • 8% Neutral • 8% Disagree		
22	Dupilumab may be preferred in moderate-to-severe AD patients with severe comorbidities, such as end-stage organ disease/dysfunction, or cardiovascular and venous thromboembolism risk factors.	✓ **Consensus reached** • **42% Strongly Agree** • **41% Agree** • 17% Neutral		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
23	Dupilumab is recommended for elderly patients with moderate-to-severe AD (aged ≥65 years) who require systemic treatment.	✗ **Consensus not reached; statement reformulated** • **42% Strongly Agree** • **33% Agree** • 17% Neutral • 8% Disagree	Based on the available evidence, dupilumab is considered safe and effective in elderly patients compared with conventional systemic agents.	✓ **Consensus reached** • **33% Strongly Agree** • **67% Agree**

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
24	Dupilumab should be used with caution in patients who are pregnant or lactating due to the lack of safety/toxicity data in this subpopulation.	✓ **Consensus reached** • **33% Strongly Agree** • **67% Agree**		
Novel Treatments (Biologic – Adverse Events)				
25	Dupilumab-induced conjunctivitis can occur during treatment in AD patients. However, topical treatment with anti-inflammatory eyedrops can be considered for the management of conjunctivitis in selected cases, without the need to discontinue dupilumab treatment.	✓ **Consensus reached** • **58% Strongly Agree** • **42% Agree**		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
26	In severe or persistent cases of dupilumab-induced conjunctivitis, referral to an ophthalmologist is recommended.	✓ **Consensus reached** • **83% Strongly Agree** • **17% Agree**		
27	For AD patients with a history of recurrent or moderate-to-severe eye inflammation, or ocular surface disorders such as conjunctivitis or keratitis, consider consulting an ophthalmologist before starting treatment with dupilumab.	✓ **Consensus reached** • **50% Strongly Agree** • **42% Agree** • 8% Neutral		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
Novel Treatments (Biologic – Screening and Monitoring)				
28	There is no routine pre-treatment laboratory screening recommended prior to starting dupilumab. However, a baseline full blood count may be considered. While safety monitoring is recommended every 3–6 months, there is no requirement for the use of specific biochemical or instrumental exams.	✗ **Consensus not reached; statement reformulated** • **25% Strongly Agree** • **42% Agree** • 8% Neutral • 17% Disagree • 8% Strongly Disagree	There is no routine pre-treatment laboratory screening recommended prior to starting dupilumab.	✓ **Consensus reached** • **17% Strongly Agree** • **75% Agree** • 8% Disagree

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
29	Live attenuated vaccines should be avoided while on dupilumab treatment. Therefore, screening for age-appropriate vaccinations should be conducted at least 4 weeks prior to starting biologic treatment for AD patients.	✓ **Consensus reached** • **25% Strongly Agree** • **67% Agree** • 8% Neutral		
30		**New statement formulated**	There is no requirement for specific laboratory tests to monitor AD patients using dupilumab.	✓ **Consensus reached** • **25% Strongly Agree** • **67% Agree** • 8% Neutral
Novel Treatments (Biologic – Other Biologic Recommendations)				

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
31	Rituximab, omalizumab and ustekinumab treatment are not recommended for use in AD patients due to lack of evidence for their efficacy.	✓ **Consensus reached** • **50% Strongly Agree** • **50% Agree**		
Novel Treatments (Janus Kinase Inhibitors [JAKi] – Treatment Selection)				
32	JAKi (baricitinib, abcrocitinib, upadacitinib) can be considered for first-line systemic treatment in certain adults with moderate-to-severe AD.	✓ **Consensus reached** • **58% Strongly Agree** • **34% Agree** • 8% Disagree		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
33	JAKi systemic treatments can be considered when fast-acting treatments are required.	✓ **Consensus reached** • **58% Strongly Agree** • **42% Agree**		
34	JAKi treatment could be used as an option in moderate-to-severe AD patients with a history of severe ocular surface disease.	✓ **Consensus reached** • **42% Strongly Agree** • **58% Agree**		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
35	JAKi (abrocitinib and upadacitinib) may be considered for adolescents with moderate-to-severe AD (12–18 years old).	✓ **Consensus reached** • **58% Strongly Agree** • **25% Agree** • 17% Neutral		
36	In moderate-to-severe AD patients with latent tuberculosis, JAKi treatments should only be used after the latent tuberculosis has been adequately treated or in consultation with relevant tuberculosis specialists.	✓ **Consensus reached** • **50% Strongly Agree** • **50% Agree**		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
37	The use of JAKi in combination with other potent immunosuppressants, such as ciclosporin, is not recommended in AD treatment as it might cause an overly suppressed immune system and increased risk of infection and lymphoma.	✓ **Consensus reached** • **34% Strongly Agree** • **50% Agree** • 8% Neutral • 8% Disagree		
38	JAKi treatment should not be used during pregnancy, in patients planning for pregnancy or breastfeeding patients.	✓ **Consensus reached** • **58% Strongly Agree** • **34% Agree** • 8% Neutral		

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
39	JAKi treatment should be used with caution in the following patient groups: patients aged ≥50 years old; patients aged <18 years old; patients with elevated baseline malignancy risk (e.g. personal/family history, smokers); presence of ≥1 cardiac risk factor (e.g. hypertension, hyperlipidemia, diabetes).	✗ **Consensus not reached; statement reformulated** • **17% Strongly Agree** • **50% Agree** • 33% Disagree	JAKi treatment should be used with caution in the following patient groups: patients aged ≥65, patients at increased risk of major cardiovascular problems (stroke or myocardial infarction), smokers or patients who had smoked for a long time in the past, patients at increased risk of cancer and patients with risk factors for venous thromboembolism.	✓ **Consensus reached** • **50% Strongly Agree** • **50% Agree**

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
Novel Treatments (Janus Kinase Inhibitors [JAKi] – Screening and Monitoring)				
40	Prior to JAKi treatment initiation, testing for hepatitis B, hepatitis C, human immunodeficiency virus and tuberculosis should be conducted. Screening for a history of varicella/zoster infections and an evaluation of risk factors for venous thromboembolism should also be performed.	✗ **Consensus not reached; statement reformulated** • **33% Strongly Agree** • **42% Agree** • 8% Neutral • 17% Disagree	Prior to JAKi treatment initiation, routine screening for hepatitis B, hepatitis C, and tuberculosis should be conducted. Screening for HIV should be conducted in at-risk individuals.	✓ **Consensus reached** • **50% Strongly Agree** • **50% Agree**

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
41	Laboratory screening of baseline full blood count (including a differential white cell count), liver enzymes (especially transaminases), renal function and lipid levels is recommended before JAKi treatment initiation, at 3 months after JAKi treatment initiation and then periodically in accordance with routine patient management.	✗ **Consensus not reached; statement reformulated** • **33% Strongly Agree** • **34% Agree** • 8% Neutral • 25% Disagree	In addition to routine infective screening, pre-treatment laboratory screening of baseline full blood count (including a differential white cell count), liver enzymes (especially transaminases), renal function and lipid levels is recommended before JAKi treatment initiation.	✓ **Consensus reached** • **25% Strongly Agree** • **75% Agree**

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
42	Live attenuated vaccines should be avoided while on JAKi treatment. Specifically, inactivated herpes zoster vaccination is recommended to eligible patients at least 4 weeks prior to starting JAKi treatment.	✗ **<u>Consensus not reached; statement reformulated</u>** • **17% Strongly Agree** • **33% Agree** • 33% Neutral • 17% Disagree	Live attenuated vaccines should be avoided while on JAKi treatment. However, inactivated herpes zoster vaccination could be considered for all patients.	✓ **<u>Consensus reached</u>** • **33% Strongly Agree** • **59% Agree** • 8% Disagree

No.	Round 1 Statement	Round 1 Outcome (% of panelists)	Round 2 Statement	Round 2 Outcome (% of panelists)
43		**New statement formulated**	After JAKI treatment initiation, regular laboratory screening should be carried out as part of routine patient management.	✓ **Consensus reached** • **25% Strongly Agree** • **75% Agree**

Abbreviations: AD: atopic dermatitis; HIV: human immunodeficiency virus; JAKi: Janus Kinase inhibitors.