

Atopic Dermatitis: An Evidence-Based Treatment Update

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Abstract

Background Atopic dermatitis (AD) is a common inflammatory disorder of skin with significant comorbidities. AD care often requires a combination of treatment approaches, including emollients, topical steroids, systemic immunosuppressants and/or phototherapy.

Purpose Our purpose was to review recent randomized controlled trials (RCT) and systematic reviews of AD treatments.

Methods A MEDLINE search was performed focusing on RCTs of AD treatments, with a sample size ≥ 15 , and systematic reviews published from 2011 to 2013, limited to the English language. A total of 53 manuscripts met the inclusion/exclusion criteria, including 44 RCTs and nine systematic reviews.

Results Investigator-initiated RCTs support the use of the systemic agents cyclosporine, methotrexate, azathioprine and mycophenolate mofetil. In one RCT, petrolatum was found to be as effective as creams containing ceramides or glycyrrhetic acid. Additional therapeutic approaches supported by RCTs include balneotherapy, oral and/or topical probiotics, nutritional interventions, vitamin D with or without vitamin E supplementation, as well as several new topical and complementary medicines.

Conclusions Advances have been made with respect to AD treatment in the past few years through the use of well designed RCTs and comparative efficacy studies. However,

more well designed RCTs and investigator-initiated studies are needed in order to improve the care of AD patients.

1 Introduction

Atopic dermatitis (AD) or eczema is a chronic inflammatory disorder of the skin that can be a significant cause of morbidity. The 2010 Global Burden of Disease Study ranked AD as the skin disease with the greatest health burden worldwide [1]. The prevalence of AD in the USA is 10.7 % for children [2], with 26.0 and 7.0 % reportedly having moderate and severe disease, respectively [3]. Previous studies have suggested that the prevalence of AD is much lower in adults, at ~ 3 % [4]. However, a recent US population-based study found that the prevalence of AD overall and AD with asthma or other atopic disease in adults is 10.2 and 3.2 %, respectively [5]. These epidemiologic data draw attention to the importance of developing effective therapies for AD in both adults and children alike.

Numerous treatment approaches exist for AD, including topical and systemic agents, phototherapy and anti-pruritic drugs. Despite this, the number of medications approved by the US Food and Drug Administration for the treatment of AD is quite limited. As such, new and more effective treatment approaches are needed. Further, much of the evidence for commonly used therapeutic modalities in AD is limited to anecdotal reports, case series or retrospective studies [6]. Thus, a greater emphasis on randomized controlled trials (RCTs) and systematic reviews that address heterogeneity and methodological shortcomings is warranted to improve the quality of evidence. This systematic review examines recent RCTs and systematic reviews in the literature in order to provide an evidence-based update on treatments for AD.

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2 Methods

A systematic review of the medical literature was performed following the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement criteria [7]. A search of MEDLINE from January 2011 to August 2013 was conducted to identify studies reporting the treatment of AD. Inclusion and exclusion criteria were set before the search of medical literature was conducted. A search was performed using the terms 'atopic dermatitis' or 'atopic eczema' and 'treatment.' The results of these searches were limited to the English language, human subjects, and RCTs and/or systematic reviews. Manual review of the abstracts and full articles of the resultant pool of articles was then carried out to extract relevant studies involving clinical trials investigating treatment of AD. The inclusion criteria for RCTs were that the study was randomized, a clinical trial, with a sample size ≥ 15 patients, which primarily assessed clinical improvement of AD severity. All relevant systematic reviews were included in this review. The exclusion criteria were that studies primarily concerned with the epidemiology, prevention and biomarkers of AD and treatment of asthma and/or other non-atopic disorders and retraction of the manuscript. Level of evidence was determined by the United States Preventive Services Task Force system [8]; all RCTs are level I evidence. Quality of evidence was also assessed for systematic reviews using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) system [9].

3 Results and Implications for Future Research

The initial medical subject headings (MeSH) search using the terms 'atopic dermatitis' and 'treatment' yielded a total of 132 articles. Of these articles, 44 RCT and nine systematic reviews met inclusion criteria for this review. Searching by the terms 'atopic eczema' and 'treatment' yielded an additional 11 articles, none of which met inclusion criteria for this review.

Large-scale RCTs are the gold standard for evaluating the efficacy of novel therapeutic approaches for AD. However, investigator-sponsored studies of this type are limited in number as they are costly and difficult to execute. Several important studies have recently examined the comparative efficacy and safety of more established systemic immunosuppressive medications. Multiple studies and systematic reviews have demonstrated a therapeutic role for a variety of topical medications and medical devices, nutritional supplementation, probiotics and novel phototherapeutic approaches as primary and/or adjunctive modalities of AD care (Table 1).

3.1 Systemic Immunosuppressants

Three RCTs examined the comparative efficacy and safety of oral methotrexate, cyclosporine, azathioprine and mycophenolate mofetil [10–12]. Haeck et al. [12] compared mycophenolate mofetil and cyclosporine in a 12-month investigator-blinded study of 55 adults with AD refractory to topical therapy. They found that both therapies had similar efficacy in improving AD severity and reducing impairment of quality of life. Mycophenolate mofetil appeared to induce more prolonged improvement of AD than cyclosporine, although patients taking mycophenolate mofetil required more frequent rescue courses of prednisone during treatment. They had similar adverse-event profiles, though only cyclosporine was associated with characteristic hypertrichosis (62 %) and gingival hypertrophy (19 %).

Schram et al. [11] compared methotrexate and azathioprine in an investigator-blinded study of 43 adults with severe AD. They found that both therapies had similar efficacy in improving AD severity and reducing impairment of quality of life by 12 weeks. They had similar adverse-event profiles with no serious adverse events occurring in either group, though abnormalities in the blood count, particularly lymphocytopenia, were significantly more frequent in the azathioprine group. Schram et al. [13] also performed a systematic review of RCTs, cohort studies and case series of the off-label use of azathioprine in dermatology, including ten articles on AD (Table 2). They found that azathioprine results in moderate improvement of moderate to severe AD, but that attention should be given to safety aspects when prescribed.

Most recently, El-Khalawany et al. [10] compared low-dose regimens of methotrexate (7.5 mg/week) and cyclosporine (2.5 mg/kg/day) for 12 weeks in a non-blinded study of 40 children and adolescents with severe AD. They found that both therapies had similar efficacy in improving AD severity, with peak benefit at 12 weeks and no significant differences in disease severity or severity reduction at 24 weeks. Both medications were associated with a variety of reversible adverse events, none of which required discontinuation or decrease of the dose.

Together, these studies provide evidence for the efficacy of cyclosporine, methotrexate and mycophenolate mofetil. Anecdotally, there are some patients who respond well to one of these medications and not the others. Future research into the predictors of patients' response to these agents is needed and may help guide clinicians' choices for the most effective option. Additionally, potential risk of lymphomas and other cancers due to immunosuppression, as well as the role of folate co-administration in the therapy of methotrexate for AD needs to be explored.

Table 1 Randomized controlled trials of atopic dermatitis treatments published in 2011–2013

References	Treatment	Study design	Number of pts	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Systemic therapy									
El-Khalawany et al. [10]	Low-dose MET vs. CSP	mc, ran, nb	40	24	Severe AD, SCORAD	SCORAD	8–14 y	CSP and MET resulted in improved AD severity. No sig diff in outcomes between the two tx	MET: Anaemia, fatigue, abnormal LFTs, nausea and vomiting, glossitis with oral ulceration. CSP: Fatigue, leukopenia, headache, anaemia, flu-like symptoms
Schram et al. [11]	MET vs. AZA	ran, ib, parallel	43	12	Severe AD, UK WPC, RLC	SCORAD, EASI, IGA, PGA, VAS, POEM, Skindex-17	≥ 18 y; mean 40 y	MET and AZA resulted in improved AD severity. No sig diff in outcomes between the two tx	Infections, GI, exacerbation of AD, blood count abnormalities, increased liver enzyme values
Haeck et al. [12]	MMF vs. CSP	sc, ran, ib, parallel	55	48	AD with insufficient response to topical cort, HRC	SCORAD, DLQI, VAS	≥ 18 y; mean 36 y	MMF and CSP resulted in improved AD severity. No sig diff in outcomes between the two tx during maintenance phase. Some MMF but not CSP pts required rescue courses of prednisone. After medication withdrawal, AD severity increased in CSP but not MMF group	MMF: nausea, headache, fatigue, paresthesias, muscle aches, infections, abnormal lab values. CSP: as above, hypertrichosis and gingival hyperplasia
Topical therapy									
<i>Emollients</i>									
Miller et al. [15]	Petrolatum vs. prescription ceramide or glyceryrhetinic acid-containing creams	sc, ran, ib, contr	39	3	Mild–moderate AD, IGA, BSA	EASI, IGA, VAS, BSA	2–17 y	Petrolatum resulted in similar or greater improvement of AD severity vs. other creams, was 47 times more cost effective	Not listed
<i>Corticosteroids</i>									
Ruzicka et al. [17]	Mometasone furoate cream with 33 % water content vs. fatty cream	sc, db, ran, contr phase II	20	2	Mild–moderate AD, SCORAD	SCORAD	≥ 18 y	No difference of efficacy between formulations, 33 % water cream was preferred by pts over fatty cream	None
Canpolat et al. [19]	Hydrocortisone acetate vs. combined hydrocortisone acetate + mupirocin	sc, db, ran, emollient-contr	83	8	Mild–moderate AD, HRC, RLC	SCORAD, EASI	6–24 mo	HC acetate monotherapy and HC acetate + mupirocin combination resulted in improved AD severity. Combination therapy was not sig better than monotherapy	Not listed

Table 1 continued

References	Treatment	Study design	Number of pts	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
<i>Calcineurin inhibitors</i>									
Bauer et al. [21]	PIM 1 % cream	sc, ran, db, vehicle-contr	36	8	Moderate–very severe hand AD, IGA	Hand Eczema Severity Score, IGA, pt self-assessment, DLQI	≥ 18 y; mean 30–34 y	PIM was not superior to vehicle as maintenance tx of hand AD	“Mostly mild or moderate”—NS
<i>Non-steroidal agents</i>									
Patrizi et al. [24]	Cream containing sorbityl furfural palmitate	sc, db, ran, pc	60	8	Mild–moderate AD with pityriasis alba, HRC	IGA, VAS	2 mo–15 y	Cream with sorbityl furfural palmitate resulted in improved AD severity	No serious adverse events
Wu et al. [25]	15(R/S)-methyl-lipoxin A4 cream vs. mometasone furoate vs. PL	Two-centre, db, ran, pc	60	7	Mild–severe infantile acute and subacute facial AD, AAD consensus guidelines	Severity Scale Score, modified EASI score	1–12 mo	Lipoxin cream resulted in improved AD severity. Lipoxin cream slightly less effective than mometasone with longer onset of action	None
Bissonnette et al. [26]	WBI-1001 [2-isopropyl-5-((E)-2-phenylethenyl) benzene-1,3-diol (IPBD)]	mc, phase IIb, ran, db, pc	124	12	Mild–severe AD, HRC	IGA, SCORAD, EASI	18–65 y	WBI-1001 resulted in gradual improvement of AD severity and rapid improvement of pruritus	Application site irritation, contact dermatitis, papular rash, folliculitis and headache deemed related to tx. Cellulitis and acute cholecystitis deemed unrelated to tx. Abdominal pain, gastroenteritis, nasopharyngitis, URTI, back and neck pain, and cough more common in tx group, but not discussed
Emer et al. [27]	Reverse-phase formulation of 70 % lipid dispersed in 30 % water cream vs. PIM 1 % cream	sc, ran, ib, parallel	20	4	Mild–moderate AD, PGA	PGA, TLSS	14–50 y	Both tx resulted in sig improvement of AD severity. No sig diff in improvement between groups	None
Frankel et al. [28]	Ceramide-HYA emollient foam vs. PIM 1 % cream	sc, ran, ib, parallel	30	4	Mild–moderate AD, IGA	IGA, TLSS, VAS	4–69 y	Both tx resulted in sig improvement of AD severity. No sig diff in improvement between groups	None
Arenberger et al. [29]	Three combinations of topical levomenol and/or heparin vs. PL	mc, ran, db, pc	278	8	Mild–severe AD, diagnosis criteria NS	VAS, SCORAD	0.7–59 y	Combination of topical levomenol and heparin resulted in improved AD severity and pruritus vs. monotherapy or PL	Transient intensification of pruritus

Table 1 continued

References	Treatment	Study design	Number of pts	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Udompataikul and Srisatwaja [30]	Moisturizer containing licochalcone A vs. hydrocortisone lotion	sc, ib, ran, parallel	30	6	Mild to moderate AD, HRC, SCORAD	SCORAD	2–15 y	Both tx resulted in improved AD severity. No sig diff in outcomes between the two tx	None
Draeos [32]	Topical HYA vs. ceramide	sc, ran, db, split-body contr	20 females	4	Mild–moderate AD, IGA	IGA	≥ 18 y	Both topical HYA and ceramides resulted in improvement of AD. HYA more effective and preferred by pts over ceramide	Not listed
Herzog et al. [35]	Nalmefene cream	mc, ran, db, vehicle-contr cross-over	62	8 h per episode of pruritus	Moderate–severe AD, VAS, IGA	Sum of pruritus intensity difference from 0 to 4 h, EASI, IGA	Adults; mean 39 y	Nalmefene cream did not result in sig improvement of pruritus, EASI or IGA vs. vehicle	Erythema, oedema
Probiotics									
Han et al. [36]	Oral <i>Lactobacillus plantarum</i> CJP133	sc, ran, db, pc	118	16	AD, HRC	SCORAD	1–13 y	AD severity decreased more in probiotic group than in PL group	
Drago et al. [37, 38]	Oral <i>Lactobacillus salivarius</i> LS01	sc, ran, db, pc	38	20	Moderate–severe AD, AAD consensus guidelines, SCORAD	SCORAD, DLQI	18–46 y	AD severity decreased more in probiotic group than in PL. Probiotic tx resulted in decreased staphylococci load vs. PL	
Iemoli et al. [39]	Combination of oral <i>Lactobacillus salivarius</i> LS01 and <i>Bifidobacterium breve</i> BR03	sc, ran, db, pc	48	20	Mild–severe AD, AAD consensus guidelines, SCORAD	SCORAD, DLQI	Adults, mean 30–32 y	AD severity and QOL impairment decreased more in probiotic group vs. PL	None
Gore et al. [83]	Oral <i>Lactobacillus paracasei</i> or <i>Bifidobacterium lactis</i> combined with extensively hydrolyzed formula	sc, ran, db, pc	208	36	Mild–severe AD, physician diagnosis, SCORAD ≥ 10	SCORAD	3–6 mo	Probiotic therapy did not result in sig improvement of AD vs. PL	Green loose stools, increased vomiting, feed refusal related to study formula

Table 1 continued

References	Treatment	Study design	Number of pts	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Wu et al. [42]	Oral fructo-oligosaccharide with or without <i>Lactobacillus salivarius</i>	sc, ran, db, pc	60	10	Moderate-severe AD, HRC, SCORAD	SCORAD	2–14 y	Combination therapy with fructo-oligosaccharide and <i>Lactobacillus salivarius</i> resulted in greater improvement of AD severity than fructo-oligosaccharide alone	Mild diarrhoea
Moroi et al. [41]	Topical cort and TAC with or without oral heat-killed <i>Lactobacillus paracasei</i> K71	sc, ran, db, pc	34	12	Mild-moderate AD, JDA scoring system	JDA scoring system, VAS, Skindex-16	20–65 y	AD severity and QOL impairment decreased in probiotic group but not in PL	Nausea, headache
Torii et al. [40]	Oral <i>Lactobacillus acidophilus</i> L-92	mc, db, ran, pc	60	8	Mild-severe AD, ADASI	ADASI	1–12 y	Probiotic was associated with sig improvement of AD extent/severity; PL was not	None
Shafiei et al. [43]	Conventional AD care with or without oral synbiotic powder	sc, ran, db, pc	41	8	Moderate-severe AD, HRC, SCORAD	SCORAD	1–36 mo	No sig diff in improvement of AD severity between synbiotic and control groups	None
Cognitive Schut et al. [63]	CBT	sc, ran, nb, contr	28	10–14	Mild-severe AD, SCORAD	SCORAD	Mean 22–23 y	CBT did not result in improved AD severity, CBT resulted in reduced cortisol awakening response, more calmness and lower cortisol levels	Not listed
Bostoen et al. [62]	Bi-weekly 2-h disease educational programme	sc, ran, ib, contr	21 with AD	36	Mild-severe AD, dermatologist diagnosis	SCORAD, EASI	21–63 y	Educational intervention did not result in sig improvement of AD severity or QOL impairment vs. control	Not listed
Bae et al. [64]	Progressive muscle relaxation	sc, ran, nb conventional therapy contr	25	4	Mild-severe AD, HRC, EASI	EASI, serum biomarkers	12–40 y	Progressive muscle relaxation did not result in sig improvement of AD severity vs. control	Not listed
Armstrong et al. [61]	Online video vs. pamphlet education programme	sc, ran, nb, parallel	80	12	Mild-severe AD, HRC	POEM	≥ 18 y; mean 46–50 y	Online video education resulted in greater improvement of AD severity than pamphlet group	Not listed

Table 1 continued

References	Treatment	Study design	Number of pts	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Nutritional interventions									
Amestajani et al. [46]	Cholecalciferol	sc, ran, db, pc	60	8	Mild–severe AD, HRC, SCORAD	SCORAD, 3-item score	≥ 14 y; mean 23 y	Vitamin D supplementation resulted in improved AD severity for mild, moderate and severe disease	Not listed
Jin et al. [49]	Partially hydrolyzed cow's milk vs conventional cow's milk formula	sc, ran, db, contr	113	12	Mild–moderate AD, HRC, BSA	JDA scoring system, SCORAD	1–6 mo	Partially hydrolyzed cow's milk resulted in improved AD severity; conventional cow's milk did not	Bad taste
Javanbakht et al. [47]	Cholecalciferol and/or alpha-tocopherol	sc, db, ran, pc	52	8	Moderate–severe AD, HRC, SCORAD	SCORAD	13–45 y	Combination vitamin D and E supplementation resulted in greater improvement of AD severity than either vitamin alone or PL	Not listed
Herbal remedies									
Ramírez-Bosca et al. [54]	Polypodium leucotomos extract	mc, ran, db, pc	105	24	Moderate AD, HRC, SCORAD	SCORAD, no. of flares	2–17 y	Herbal extract did not result in sig improvement of AD severity	Bronchospasm episode, lip swelling, chickenpox, cold, tonsillitis, cough and cold
Choi et al. [51]	Chinese herbal remedy: Hwang-Yeon-Hae-Dok-San (TJ-15) with or without Ouryung-San (TJ-17)	sc, db, ran, active-contr	24	4	HRC, dampness-heat pattern type AD	SCORAD, EASI	5–32 y	TJ-15 and TJ-17 resulted in improvement of AD severity. No sig improvement of TJ-15 and TJ-17 combination therapy over TJ-15 monotherapy	None
De Belilovsky et al. [53]	Sunflower oleodistillate 2 % cream vs. topical hydrocortisone butyrate-propionate 1 mg/g steroid cream	sc, nb, ran, parallel	80	3	Mild–severe AD, SCORAD	SCORAD, Infant Dermatitis QOL, Dermatitis Family Impact Questionnaire	3 mo–4 y	Both tx resulted in significant improvement of AD severity. No sig diff in improvement between groups	
Hon et al. [55]	Concoction of five Chinese herbal extracts orally	sc, db, ran, pc	85	16	Moderate–severe AD, HRC, SCORAD	SCORAD	5–21 y	No sig improvement in AD severity by herbal extract therapy over PL	“uncommon, mild, self-limiting”—though NS
Cheng et al. [52]	Oral Chinese herbal product (Xiao-Feng-San)	sc, db, ran, pc	71	12	Severe AD, HRC, BSA	Standardized disease activity scoring system	≥ 3 y; mean 13 y	Chinese herbal product resulted in sig improvement of AD activity; PL did not	Bad taste

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References	Treatment	Study design	Number of pts	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Phototherapy									
Byun et al. [70]	Full spectrum light phototherapy vs. emollient cream	sc, nb, ran, emollient contr	38	8	Moderate-severe AD, HRC, SCORAD	SCORAD	25-48 y	Full spectrum light phototherapy resulted in significant improvement of AD activity; PL did not	Erythema, dryness, pruritus, burning, transient AD exacerbation
Heimlin et al. [68]	Balneootherapy vs. NBUVB therapy	mc, nb, ran, parallel	180	24	Moderate-severe AD, dermatologist diagnosed (criteria NS), SCORAD	SCORAD, Freiburger QOL index, Sickness Impact Profile, 6-step Likert scale	≥18 y; mean 41 y	Balneootherapy resulted in similar or greater improvement of AD severity vs. NBUVB. Response to balneootherapy occurred earlier than to NBUVB	Comparable between both therapies. Erythema, light dermatoses most common
Farina et al. [69]	Balneootherapy vs. topical cort therapy	sc, nb, ran, parallel	104	2	Mild-moderate AD, IGA, SCORAD	SCORAD, IGA, Pits' Self Global Assessment, Children's DLQI, Family Dermatitis Impact Questionnaire	1-14 y	Balneootherapy resulted in similar or slightly lower improvement of AD severity vs. topical cort	Erythema, burning sensation
Other									
Lee et al. [71]	Acupuncture	sc, ran, nb, contr	15	4	Mild-severe AD, physician diagnosis	VAS, IGA, EASI lichenification	19-79 y	Acupuncture resulted in sig improvement of pruritus and lichenification	None
Novak et al. [76]	Immunotherapy with depigmented polymerized mite extract	mc, ran, db, pc, phase III	168	72	Mild-severe AD, HRC, SCORAD	SCORAD, medication use—cumulative topical and/or systemic	18-66 y	Overall, no sig diff in improvement of AD severity in immunotherapy vs. control group. In adults with severe AD, immunotherapy resulted in greater improvement of severity than control	Flare-ups of eczematous and urticarial lesions, symptoms of rhinitis, pruritus, transient headache, asthma
Thomas et al. [74, 84]	Conventional AD care with or without ion-exchange water softener	mc, ib, ran, parallel	336	16	Mild-severe AD, UKWPC, SASSAD	SASSAD, POEM, amount of topical medication used, totally- and well-controlled weeks, Dermatitis Family Index, EQ-5D	6 mo-16 y	Water softeners provided no additional clinical benefit over conventional AD care in children	Not formally collected in the study, parental report of AD exacerbation with water softener

Table 2 Systematic reviews of atopic dermatitis treatments published in 2011–2013

References	Treatment	Inclusion criteria	Publication y	Critical review of methodology of included studies	Number of studies reviewed	Conclusions	Level ^a and quality ^b of evidence
Systemic therapy							
Schram et al. [13]	Off-label use of AZA	RCT, cohorts and case series ($n > 5$), human studies, children and adults	1950–2009	Yes	43 overall; 10 for AD	AZA results in moderate improvement of moderate–severe AD. Attention should be given to safety aspects when prescribed	Level I, high-quality evidence
Topical therapy							
Svensson et al. [20]	Topical calcineurin inhibitors vs. cort	RCT, at least 2 tx arms, children and adults	2000–2009	Yes	17	TAC 0.1 % was as or more effective than class I/II and consistently more effective than class III/IV topical cort. Class II topical cort were more effective than TAC 0.03 %. TAC resulted in more stinging than topical cort	Level I, moderate quality of evidence due to considerable heterogeneity between studies
Schmitt et al. [23]	Proactive tx with topical calcineurin inhibitors vs. cort	RCT, children and adults	All y up to 2009	Yes	9	Proactive tx with topical cort and TAC were both effective at preventing disease flares. Cort were more effective than TAC with less burning of skin	Level I, moderate quality of evidence due to considerable heterogeneity of study quality
Cognitive							
de Bes et al. [65]	Pt education interventions	RCT, received pt education, QOL reporting, children and adults	2000–2008	No	10 overall; 8 for AD, 2 for AD and psoriasis	In some studies, extended and frequent pt education sessions resulted in improved AD severity, QOL and coping with disease. Shorter education session did not result in sig improvement	Level I, low–moderate quality of evidence as quality of studies was not reviewed
Nutritional interventions							
Bath-Hextall et al. [50]	Dietary supplements	RCT, physician diagnosed AD, children or adults	Yr up to 2011	Yes	11	Two studies of fish oil showed modest benefit, but many outcomes were explored. No convincing evidence for dietary supplementation in AD	Level I, low–moderate quality of evidence due to inconsistency of results and heterogeneity of studies
Herbal remedies							
Tan [56]	Chinese herbal therapies	RCT, severity or QOL measures	1992–2010	Yes	7 overall; 6 pc, 1 parallel design	Chinese herbal (Xiao Feng San, Sheehan's formula, Pentaherb, Jian Pi Shen Shi and/or Hochu-ekki-to) tx reported in decreased erythema, surface damage score, pruritus, sleep impairment and QOL	Level I, moderate quality of evidence due to heterogeneity of studies
Other							

Table 2 continued

References	Treatment	Inclusion criteria	Publication y	Critical review of methodology of included studies	Number of studies reviewed	Conclusions	Level ^a and quality ^b of evidence
Sher et al. [22]	Antipruritic effects of topical calcineurin inhibitors, cort, antihistamines vs. systemic immunosuppressants and antihistamines	ran, pg, crossover and left-right comparison ($n > 20$)	1990–2009	No	52 overall; 42 for topical and 10 for oral tx	Topical calcineurin inhibitors (PIM, TAC 0.03 and 0.1 %) were as effective as topical cort (lotions, creams and ointments). Topical antihistamines were slightly less effective. One RCT found oral anti-histamines were NOT effective	Level I, low–moderate quality of evidence as quality of studies was not reviewed
Bae et al. [77]	Specific allergen immunotherapy	RCT, pc	All yr up to 2012	Yes	8 RCT; 7 db, 1 single-blind	Subcutaneous immunotherapy had a positive overall effect on AD, particularly severe AD. Sublingual immunotherapy had no significant effect on AD	Level I, moderate quality of evidence due to study heterogeneity
Compalati et al. [78]	Specific allergen immunotherapy	RCT, observational studies with control group	31 Dec 2006–31 Dec 2011	Yes	4 overall; 2 RCT, 2 observational	Subcutaneous and sublingual immunotherapy improved AD severity or symptoms	Level II-2, low quality of evidence with non-RCT and heterogeneity of studies

AD atopic dermatitis, AZA azathioprine, cort corticosteroids, db double-blind, pc placebo-controlled, pg parallel-group, PIM pinacrolimus, pt patient, QOL quality of life, ran randomized, RCT randomized controlled trial, sig significant, TAC tacrolimus, tx treatment, y year

^a US Preventive Services Task Force level of evidence: I (highest): RCT or meta-analysis; II-1: controlled-trial /quasi-experiment; II-2: cohort or case-control studies; II-3: case-series; III: case report

^b Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading quality of evidence: high quality—further research is very unlikely to change our confidence in the estimate of effect. Moderate quality—further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality—further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality—any estimate of effect is very uncertain

3.2 Topical Therapy

3.2.1 Emollients

Topical emollients are a mainstay of AD care. They act by repairing the skin barrier, increasing water content, reducing transepidermal water loss, and restoring the lipid barrier's ability to hold and redistribute water [14]. In a randomized, investigator-blinded study of 39 paediatric patients, Miller et al. [15] compared petrolatum with prescription creams containing either ceramides or glycyrrhethinic acid in the management of mild to moderate AD. They found that petrolatum resulted in a 64 % improvement of the Eczema Area and Severity Index (EASI) score at 3 weeks. Further, petrolatum was equally effective at reducing AD severity, extent and pruritus after 1 and 3 weeks, as well as dramatically more cost effective. The comparable efficacy of petrolatum to these other agents is likely due to its occlusive properties. However, some patients may prefer a lotion or cream-based formulation. More comparative efficacy and patient preference studies are needed to confirm this finding. Moreover, future industry-sponsored trials of novel emollients might be improved by including a subset of patients being treated with petrolatum.

3.2.2 Corticosteroids

Topical corticosteroids remain the first-line therapy for AD flares [16]. A recent RCT demonstrated efficacy of a novel formulation of mometasone furoate cream with 33 % water content in the treatment of mild to moderate AD in adults [17]. Topical and systemic antibiotics are often required for cutaneous bacterial infections associated with AD, but have questionable utility for treatment of AD per se [18]. A recent double-blind RCT investigated the efficacy of combination topical hydrocortisone acetate and mupirocin versus corticosteroid alone or emollients for long-term therapy of mild to moderate AD [19]. Combination therapy did not offer any additional benefits beyond topical corticosteroid monotherapy.

3.2.3 Calcineurin Inhibitors

A systematic review of 17 RCTs comparing topical calcineurin inhibitors with corticosteroids found that tacrolimus 0.1 % was as effective or even more effective than class I/II topical corticosteroids in children and adults [20]. However, class II topical corticosteroids were more effective than tacrolimus 0.03 %. Further, tacrolimus resulted in more stinging overall than topical corticosteroids. Of note, a recent randomized double-blind vehicle-controlled study of 36 adults with moderate to severe

atopic hand dermatitis found that pimecrolimus cream was not effective [21].

A systematic review of 42 RCTs of topical and ten RCTs of oral treatments in AD found that topical calcineurin inhibitors, including pimecrolimus and tacrolimus 0.03 and 0.1 %, had similar anti-pruritic effects as topical corticosteroids, irrespective of the vehicle [22]. Topical antihistamines were slightly less effective than corticosteroids or calcineurin inhibitors, while one RCT of oral antihistamines found no improvement of pruritus from AD.

The above-mentioned studies used topical corticosteroids and/or calcineurin inhibitors as a once- or twice-daily treatment for active AD. However, recent evidence supports the use of proactive treatment with topical agents, i.e. preemptive use of topical agents during quiescent periods to prevent future AD flares. A recent systematic review of nine RCTs found that proactive treatment with topical corticosteroids and tacrolimus was effective at preventing disease flares [23]. However, corticosteroids were more effective than tacrolimus and resulted in less burning of the skin. These studies provide a moderate to high level of evidence, though there was considerable heterogeneity of study quality.

3.2.4 Non-Steroidal Agents

Given the adverse effects associated with chronic topical steroid usage, such as cutaneous atrophy and tachyphylaxis, numerous groups have looked for non-steroidal agents with good efficacy in the treatment of AD. Several novel topical treatments have been shown in recent RCTs to be effective in the treatment of AD, including sorbityl furfural palmitate [24], 15(R/S)-methyl-lipoxin A4 cream [25], 2-isopropyl-5-([E]-2-phenylethenyl) benzene-1,3-diol (benvitimod or WBI-1001) [26], medical device preparations consisting of reverse-phase formulation of 70 % lipid dispersed in 30 % water cream and a ceramide-hyaluronic acid emollient foam [27, 28], combination of topical levomenol and heparin [29] and licochalcone A [30]. Hyaluronic acid has recently gained attention as a potential therapeutic option for AD as it is both a humectant and able to bind to CD44 on keratinocytes, resulting in the formation and secretion of lamellar bodies [31]. A double-blind RCT of 20 women found that an emollient foam containing hyaluronic acid was more effective as measured by the IGA and preferred by patients over ceramide-containing creams [32].

Since opioid agonists often cause itch, and systemic opioid antagonists have been found to reduce itch [33, 34], opioid antagonists have been suggested as a potential therapeutic target for the management of itch in AD. However, a double-blind, vehicle-controlled RCT of topical nalmefene (an opioid antagonist) in 62 US adults with

moderate—severe AD demonstrated no efficacy in the treatment of itch [35].

3.3 Probiotics

A number of studies have found associations between gut microbes and atopic disease, which makes probiotics attractive candidates for adjunctive therapy in AD. Multiple well designed RCTs have demonstrated significant improvements in severity and extent of AD and/or impairment of quality of life by oral *Lactobacillus* on AD severity, including *L. plantarum* CJLP133 [36], *L. salivarius* LS01 [37, 38], combination of *L. salivarius* LS01 and *Bifidobacterium breve* BR03 [39] and *L. acidophilus* L-92 [40]. Similarly, topical *L. paracasei* K71 combined with conventional topical AD therapy (corticosteroid and/or tacrolimus) resulted in greater improvement of AD severity and impairment of quality of life than conventional therapy alone [41].

Synbiotic therapy is a mixture of prebiotics, i.e. non-digestible oligosaccharides, and probiotics. A recent RCT found that combination oral fructo-oligosaccharide with *L. salivarius* resulted in significant improvement of moderate to severe AD in children [42]. However, topical synbiotic powder conferred no additional benefit over placebo with conventional AD care alone [43]. Together, these studies provide considerable evidence in support of adjunctive oral and topical probiotic and oral synbiotic therapy. However, these results should be interpreted cautiously as prior systematic reviews found no evidence to support the efficacy of probiotics for the treatment of AD [44]. More studies are needed to standardize doses, strains and preparations and to identify the most safe and effective combination therapy.

3.4 Nutritional Supplementation

Several studies found an association between vitamin D deficiency and inflammatory skin disorders, such as AD [45]. However, the extant data are conflicting with some reports of high vitamin D levels being associated with AD [45]. Recent studies provide evidence to support oral vitamin D supplementation in AD [46, 47]. A double-blind placebo-controlled RCT of 1,600 international units (IU) per day of oral cholecalciferol found that supplementation resulted in improved AD severity for adolescents and adults with mild, moderate or severe disease [46]. Further, a double-blind placebo-controlled RCT of 1,600 IU per day of oral cholecalciferol with or without 600 IU of tocopherol found that combination supplementation resulted in greater improvement of AD severity for adolescents and adults with moderate or severe disease compared with either alone or placebo [47].

The role of diet and nutrition in AD has received much attention over the past few decades, though this area

remains controversial [48]. A recent double-blind RCT of 113 infants with mild to moderate AD found that a 12-week diet consisting of hydrolyzed cow's milk resulted in improved disease severity, whereas conventional milk formula did not [49].

However, a recent Cochrane Skin Group systematic review of 11 RCTs of dietary supplementation in physician-diagnosed AD found little convincing evidence for the use of oral zinc phosphate, selenium with or without vitamin E, vitamin D and/or vitamin E, pyridoxine, sea buckthorn seed or pulp oil, hempseed oil, sunflower oil or docosahexaenoic acid (DHA) [50]. They did find two studies that demonstrated modest benefit of fish oil on AD, but these studies were of poor methodological quality. More high-quality studies of dietary interventions in AD are needed before they can be recommended in clinical practice.

3.5 Herbal Remedies

A variety of herbal remedies have recently been shown to be effective in the treatment of AD [51–53]. A double-blind placebo-controlled RCT of Chinese herbal remedies Hwang-Yeon-Hae-Dok-San and Ou-Ryung-San in 24 children and adults found that both were effective at treating AD without any synergic effects [51]. Similarly, a double-blind placebo-controlled RCT of 71 children with severe AD found that the Chinese herbal product Xiao-Feng-San resulted in significant improvement of AD activity compared with placebo [52]. A non-blinded RCT of 80 children with AD found that sunflower oleodistillate 2 % cream was as effective as a topical hydrocortisone butyro-propionate 1 mg/g cream [53]. In contrast, a couple of herbal extracts were not found to be effective in the treatment of AD, including polypodium leucotomas extract [54] and a concoction of five Chinese herbal extracts [55].

A systematic review of seven RCTs found that Chinese herbal therapies, including Xiao Feng San, Sheehan's formula, Pentaherb, Jian Pi Shen Shi and/or Hochu-ekki-to, resulted in decreased erythema, surface damage score, pruritus, sleep and quality of life impairment from AD [56]. However, while some herbal preparations appear to be effective at treating AD, caution must be exercised given serious adverse events reported in previous studies and lack of standardization [57–59].

3.6 Cognitive Interventions

AD has a major impact on quality of life [3] and a high prevalence of comorbid psychological disorders [60]. Accordingly, a variety of cognitive therapeutic approaches have been studied as adjunctive therapy for AD, with varied success. A non-blinded RCT of 80 adults with AD

found that an online video intervention resulted in greater improvement of AD severity than a conventional educational pamphlet [61]. Unfortunately, many cognitive approaches were not found to be effective in the treatment of AD. A novel intervention using a bi-weekly 2-h disease educational programme was not effective at improving severity or impairment of quality of life from AD in adults [62]. Further, a non-blinded RCT of cognitive behavioural therapy did not demonstrate efficacy in improving AD severity [63]. Similarly, a non-blinded RCT of progressive muscle relaxation did not demonstrate any additional benefit over conventional AD therapy alone [64].

A systematic review of ten RCTs of patient education interventions found that studies with extended and frequent patient education sessions were more likely to result in improvements in AD severity, quality of life and coping with disease [65]. In contrast, shorter education sessions did not result in significant improvement. Together, these studies highlight the need for improved strategies for patient education and behavioural interventions in AD.

3.7 Phototherapy

Phototherapy using narrow- or broad-band ultraviolet B has been used to treat extensive and refractory AD for many decades [66, 67]. Balneotherapy, in particular, involves soaking in salt water in combination with ultraviolet light exposure [68]. While it has been used for many years at the Dead Sea, it has recently been replicated in a controlled in-office setting. A couple of non-blinded RCTs demonstrated efficacy of balneotherapy in the treatment of AD with comparable efficacy to narrow-band ultraviolet B [68] and topical corticosteroid cream [69]. One approach used ≥ 4 min bathing in 10 % Dead Sea salt solution followed by 15–30 min of exposure to 311 nm UVB with dose escalation and turnovers every 4 min at 3–5 treatments per week for up to 35 treatments [68]. The other approach used thermal balneotherapy only (no light treatment), with one or two baths per day in Comano water heated to 36–37°C at a spa [69]. Both of these studies had sample sizes >100 with standardized measures of AD severity/improvement.

A novel full spectrum light phototherapy device using a continuous wavelength of 320–5,000 nm (fluence of 530 J/cm² including 121 J/cm² of UVA and 409 J/cm² of visible and infrared light for exposures of 20 min each for the anterior and posterior body twice weekly in-office for 4 weeks) was tested in a non-blinded RCT of 38 Korean adults with moderate to severe AD and found to significantly improve disease severity after 4 weeks compared with an emollient cream [70]. Approximately one-third of the patients had local cutaneous side effects, including erythema, dryness, pruritus, burning and/or transient AD exacerbation. While this modality is promising for the

treatment of AD, head-to-head studies with NBUVB or other phototherapeutic approaches have yet to be performed. This technique could potentially be practitioner dependent in results.

3.8 Miscellaneous

A non-blinded RCT of 15 adults with AD found that 4 weeks of acupuncture therapy resulted in significant improvement of pruritus and lichenification [71]. However, larger studies with investigator blinding are necessary to confirm the efficacy of this approach.

A variety of environmental variables have been associated with increased prevalence of AD in the USA [72]. A previous study suggested that ‘hard water’ may trigger or worsen AD [73]. However, a recent UK multicentre investigator-blinded RCT of 336 children with AD found no additional benefit of ion-exchange water softeners over conventional AD care [74]. This suggests that hard water may not play a major role in AD and that water softeners should not be recommended for AD care.

Previous studies suggested that dust mites might play a role in a subset of AD patients [75]. However, a recent multicentre double-blind placebo-controlled RCT of 168 adults with AD found no significant difference in improvement of AD severity between the immunotherapy and control groups (primary outcome) [76]. In secondary analyses, the authors found that immunotherapy was effective in reducing AD severity in patients with baseline severe AD. Future studies are needed to provide conclusive evidence to support or oppose dust mite immunotherapy as an effective treatment for AD.

Two recent systematic reviews of immunotherapy were performed and found conflicting results [77, 78]. A review of eight placebo-controlled RCTs found that subcutaneous specific allergen immunotherapy had a positive overall effect on AD, particularly severe disease [77]. In contrast, sublingual immunotherapy had no significant effect on AD. Another review of two RCTs and two observational studies with a control group found that both subcutaneous and sublingual specific allergen immunotherapy improved AD severity and symptoms. In both reviews, the authors noted significant heterogeneity and methodological shortcomings. Together, these studies suggest a potential role for immunotherapy in AD; however, more high-quality studies are needed before recommendations can be made for clinical practice.

4 Discussion

Recent RCTs and systematic reviews provided much needed evidence for the efficacy of cyclosporine, azathioprine,

methotrexate and mycophenolate mofetil in the treatment of severe AD. Such investigator-sponsored trials of systemic therapy for AD are vital for developing adequate treatment protocols for children and adults with severe disease; unfortunately, they are very rare. Future studies are needed to identify the determinants of response to specific agents.

Cyclosporine and methotrexate are inexpensive drugs with a proven track record in the treatment of inflammatory skin disorders, such as psoriasis [79]. Nevertheless, these drugs are non-specific immunosuppressants. Targeted therapy based on the pathogenesis of AD is the next horizon for drug development in AD. Dupilumab, a fully human monoclonal antibody to the alpha subunit of the interleukin-4 receptor, was found to be effective in the treatment of moderate to severe asthma with eosinophilia [80]. Dupilumab is currently in phase III studies for the treatment of AD, and preliminary results from phase I and II studies are promising [81].

Herbal extracts and other complementary therapeutic approaches, such as acupuncture, are becoming increasingly popular worldwide [82]. However, few of these treatments have actually been rigorously tested by RCT. The emergence of RCTs for such modalities is important to determine both their efficacy and their safety.

5 Conclusions

AD is a common disorder with significant comorbidity, including intense pruritus, erythema, lichenification, cutaneous infections and a host of other extra-cutaneous comorbidities. AD is caused by a complex interaction of barrier and immune dysfunction and environmental exposures. As such, AD care often requires a combination of treatment approaches, including emollients, topical steroids, systemic immunosuppressants and phototherapy. Advances have been made with respect to AD treatment in the past few years through the use of well designed RCTs. Systemic non-steroidal treatment options include cyclosporine, methotrexate, azathioprine and mycophenolate mofetil. Additional therapeutic approaches with level 1 evidence include balneotherapy, oral and/or topical probiotics, as well as several new topical and complementary medicines. More RCTs and comparative efficacy studies are needed for existing and newcomer AD treatments.

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