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REVIEW

A Systematic Scoping Literature Review of Publications Supporting Treatment Guidelines for Pediatric Atopic Dermatitis in Contrast to Clinical Practice Patterns

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ABSTRACT

Introduction: Treatment guidelines endorse a variety of strategies for atopic dermatitis (AD) which may vary from published data and clinical practice patterns. The objective of this review was to quantify the volume of available medical literature supporting pediatric AD treatments and compare these patterns to those recommended by published guidelines and/or clinical practice patterns.
Methods: Searches of Embase (2005–2016) and abstracts from selected meetings (2014–2016) related to AD treatment in patients younger than 17 years of age yielded references that were assessed by study design, primary treatment, age groups, and AD severity.
Results: Published literature partially supports clinical guidelines, with emollients and topical medications being the most investigated. There were disproportionately more publications for topical calcineurin inhibitors (TCI) compared with topical corticosteroids (TCS); however, the search interval may have biased the results toward treatments approved near the beginning of the time frame. In contrast, publications documenting clinical practice patterns reflect greater use of emollients and TCS (over TCI), as well as systemic corticosteroids. Data is relatively limited for long-term and combination treatment, treatment of severe AD, and patients younger than 2 years of age, and completely lacking for systemic corticosteroids.
Conclusion: This scoping review demonstrates that available medical literature largely supports published guidelines for topical therapy; however, clinical practice patterns are less aligned. There is a lack of data for older, more frequently used generic treatments, including oral antihistamines, oral antibiotics, and systemic corticosteroids. Overall, literature is lacking for long-term treatment, treatment for patients younger than 2 years of age, and for systemic treatment for severe disease.
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Keywords: Adolescents; Atopic dermatitis; Atopic eczema; Biologic agents; Children; Infants; Systemic treatment; Topical calcineurin inhibitors; Topical corticosteroids; Topical treatment

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INTRODUCTION

Atopic dermatitis (AD) is a systemic immune-mediated disease which primarily affects children with variably reported pediatric prevalence of 9–25% [1, 2]. There is a wide range of disease severity, and a variety of approaches to treatment. There are few US Food and Drug Administration (FDA)-approved treatments for AD, leaving many health care providers to prescribe off-label medications.

Several recent treatment-specific systematic reviews evaluate the efficacy and/or safety of topical calcineurin inhibitors (TCIs) [3, 4], topical corticosteroids (TCS) [4], immunotherapy [5], immunosuppressants [6, 7], omalizumab [8], emollients [9, 10], phototherapy [11–14], and wet wraps [15]. The goal of this systematic scoping review was to quantitatively and qualitatively assess the volume of medical literature supporting guidelines-based treatment as well as treatment with recently approved and late-stage investigational pharmacologic and non-pharmacologic agents for AD in pediatric patients [1, 16–25]. Because there are no pediatric-specific AD treatment guidelines, we sought to evaluate how different treatment modalities have been investigated across age groups and disease severities and how these correspond to published guidelines and studies of clinical practice patterns. The results of this analysis indicate gaps in evidence supporting current clinical management.

METHODS

A literature search for "atopic dermatitis" and specific drug-related keywords was performed using Embase on 7 November, 2016. Search terms are listed in Table 1. A review protocol does not exist. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Results were limited to those published in English after 1 January, 2005 that included newborns, infants, children, and/or adolescents. The search was supplemented with manual searches of selected meetings, which included the American Academy of Dermatology (AAD; annual and summer meetings), the American Academy of Allergy, Asthma and Immunology (AAAAI), the Society for Pediatric Dermatology (SPD)/World Congress of Pediatric Dermatology (WCPD), the European Academy of Dermatology and Venereology (EADV), the Society for Investigational Dermatology (SID)/International Investigational Dermatology (IID), and the European Society for Pediatric Dermatology (ESPD) meetings in the previous 3 years. References from meetings other than these were not included.

Results are reported as numbers of references by study design (interventional non-comparative, interventional non-randomized comparative, randomized active-controlled, randomized placebo/vehicle-controlled, randomized untreated-controlled, observational prospective cohort, observational cross-sectional, observational comparative, registry, case report/series, pooled/secondary/subgroup analysis of previously published data, retrospective chart review, retrospective cohort, and survey/interview). On the basis of keywords listed in Table 1, references were also identified by category of primary treatment investigated [TCIs, TCS, systemic immunotherapy, biologic, systemic immunosuppressant, topical phosphodiesterase 4 (PDE4) inhibitor, topical antibiotic, oral PDE4 inhibitor, topical immunotherapy, pharmacologic combination treatment, emollient, phototherapy, wet wraps, bathing, dilute bleach baths, and non-pharmacologic combination treatment]. When more than one active treatment was compared, only the primary treatment was used to categorize the reference; if a combination of treatments was used as primary treatment, the reference was categorized as "combination treatment". The potency of TCS was determined on the basis of several sources [16, 26–28], and clinical judgment in the case of non-marketed products; if a study included more than one TCS of different potency (e.g., medium potency for the body and low potency for face), it was counted for the highest potency TCS used. References that described clinical practice patterns were summarized separately. References regarding new data (i.e., not pooled/secondary/subgroup analysis of previously published data) were further categorized by AD severity as

Table 1 Search terms

Treatment	Search terms
Corticosteroid	"Topical corticosteroid*" OR "topical glucocorticoid*" OR "systemic corticosteroid*" OR "corticosteroid*" OR "glucocorticoid*" OR "hydrocortisone acetate" OR "alclometasone dipropionate" OR "clobetasone butyrate" OR "dexamethasone sodium phosphate" OR "dexamethasone valerate"/de OR "dexamethasone valerate" OR "desonide" OR "fluocortinbutylester" OR "beclomethasone dipropionate" OR "betamethasone benzoate" OR "betamethasone dipropionate" OR "budesonide" OR "desoximetasone" OR "diflucortolone valerate" OR "fluocinolone acetonide" OR "fluocinonide" OR "fluocortolone" OR "fluocortolone caproate" OR "fluticasone propionate" OR "methylprednisolone aceponate" OR "mometasone furoate" OR "prednicarbate" OR "halcinonide" OR "clobetasol propionate" OR
Calcineurin inhibitor	"Tacrolimus" OR "pimecrolimus" OR
Immunosuppressant	"Cyclosporine" OR cyclosporin OR "azathioprine" OR "methotrexate" OR "mycophenolate mofetil" OR
Oral antihistamine	"Oral antihistamine*" OR
Phototherapy	"Phototherapy" OR
Immunotherapy	Immunotherapy OR
Emollient	"Emollient*" OR
Wet wrap	"Physical therap*" OR "wet wrap*" OR "wet dressing*" OR
Bathing	"Bath*" OR
Dilute bleach baths	"Hypochlorite sodium" OR
Antibiotic	"Antibiotic agent" OR "beta lactam antibiotic" OR "flucloxacillin" OR "amoxicillin plus clavulanic acid" OR "cephalosporin" OR
Biologic	"Omalizumab" OR "ustekinumab" OR
PDE4 inhibitor	"Apremilast" OR "crisaborole" OR "e6005" OR "e-6005" OR "opa-15406" OR "opa15406"

PDE4 phosphodiesterase 4

defined within the reference (mild was analyzed together with mild-to-moderate, and moderate was analyzed with moderate-to-severe/very severe) and pediatric age groups included in the study [newborns (up to 1 month), infants (1–12 months), children (1–12 years), and/or adolescents (13–17 years)]; studies that included patients from more than one age group were counted in both groups. Interventional trials were classified by duration of treatment, or duration of follow-up for long-acting treatments like immunotherapy and biologics.

RESULTS

A total of 1579 references were retrieved from Embase and screened for relevance (Fig. 1). The following references were excluded: those not focused on treatment (i.e., risk factors for AD), those that did not specify treatment, duplicate references, encore abstracts, abstracts presenting data for which a manuscript has been published, abstracts from other meetings, non-English articles, abstract supplements, retracted articles, commentaries, review articles, and

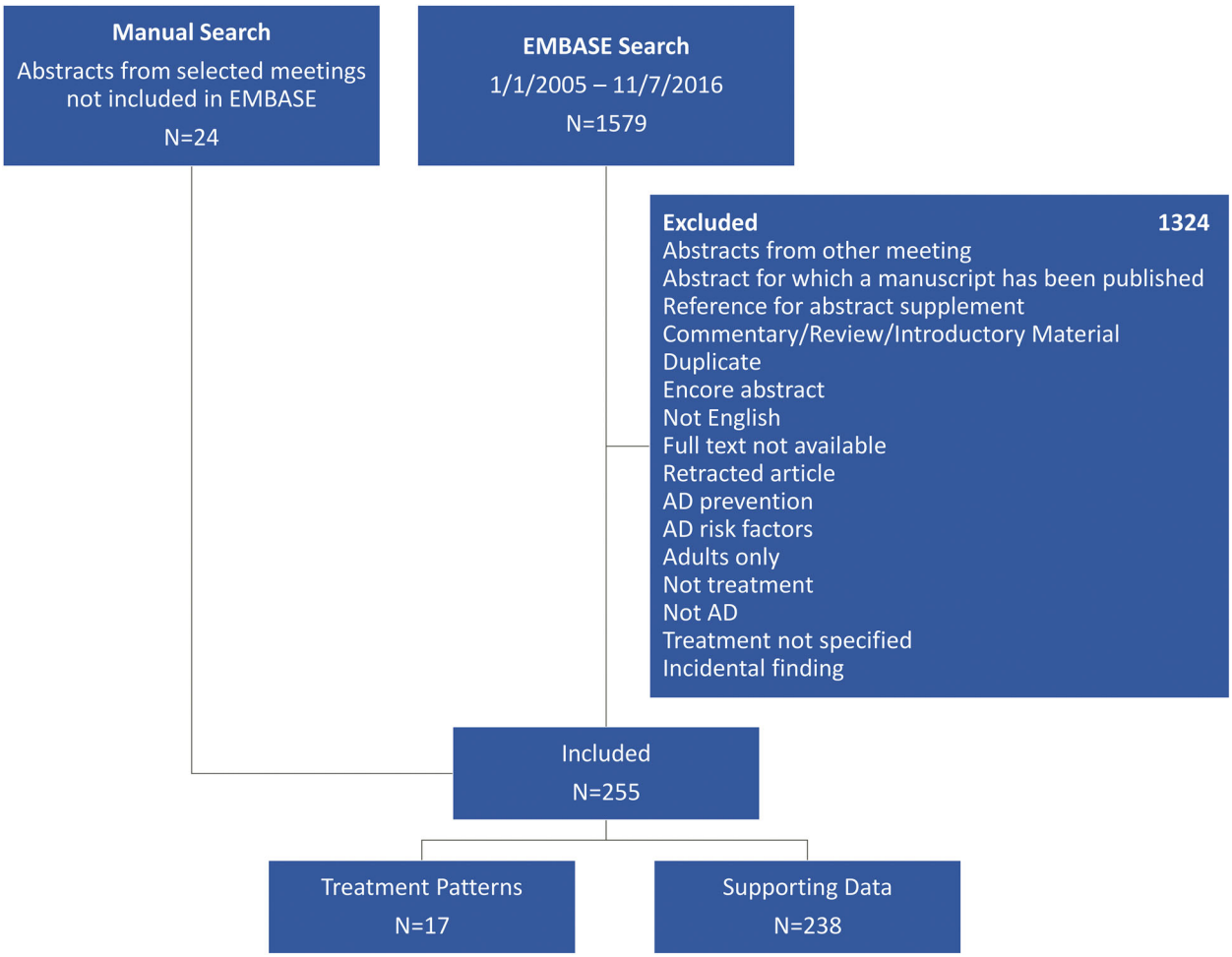

Fig. 1 PRISMA flow diagram. *AD* atopic dermatitis

introductory articles. An additional 77 articles were not included in the analysis because they focused on treatments that are not part of current guideline-based management or new therapies: pro/prebiotics ($n = 14$); clothing ($n = 10$); traditional Chinese medicine ($n = 8$); intravenous immunoglobulin ($n = 5$); cleansing, vitamin supplements, and educational interventions ($n = 4$ each); dietary elimination and balneo/crenotherapy ($n = 3$ each); oral leukotriene inhibitors, water softeners, apheresis, and phytotherapy ($n = 2$ each); and acupuncture, topical antifungal, temperature-controlled lamellar airflow, skin acidification, peroxisome proliferator-activated receptor-alpha agonist treatment, efalizumab, etanercept, chloroquine, lipoxins, adrenergic agonist treatment, hydrocolloid dressing, homeopathy, application of human milk, and high altitude treatment ($n = 1$ each). In addition, references focusing on adult patients, patient populations with mean age greater than 20 years, patient populations that were less than 40% pediatric, or prevention of AD were also excluded leaving 231 articles. Manual searches of abstracts from selected meetings yielded an additional 24 references, added to the 51 identified in the Embase search, for a total of 75 abstract references. This yields a total of 255 references for inclusion.

Of these, 17 assessed clinical practice patterns via prospective analysis, claims data, retrospective analysis, or surveys/interviews [29–45], and documented a wide variety of treatments used in

clinical practice (Fig. 2). Overall, 7 of 17 papers reported emollient use by up to 96% of patients. Seven references also reported systemic corticosteroid use in 1–25% of patients.

The most frequently used study designs in this 11-year review were interventional non-comparative and randomized controlled. The most frequently investigated medical treatments were TCIs and emollients (Fig. 3).

Treatments by AD Severity and Age Group

Published pharmacologic treatment trials varied by AD severity (Fig. 4); however, AD severity was not consistently defined. A number of studies did not prespecify severity ($n = 48$) or used surrogate definitions ($n = 8$). The pattern of severities studied was similar across age groups. Mild-to-moderate or not specified/other severity was included most frequently, and the 13- to 17-year age range was investigated most often (Fig. 5).

Publications more often investigated topical treatments for mild-to-moderate AD and systemic treatments for more severe AD (Fig. 4). Non-pharmacologic treatments were investigated primarily in mild-to-moderate AD (Fig. 4).

Across age groups, TCIs and emollients were the treatments most frequently investigated (Fig. 6). The number of treatment modalities investigated in children (1–12 years) was greater than any other age group (Fig. 6). Few studies included treatment in infants and newborns (Fig. 6). Despite the frequency of systemic corticosteroid use in clinical practice, this analysis failed to identify any publications supporting use of this treatment.

Supporting Evidence by Treatment

Topical Pharmacologic Treatments

There were 27 references that studied TCS as primary treatment [46–72]; an additional 16 used TCS as an active comparator. Of the 27 references focusing on TCS, 2 were pooled analyses of previously published studies, 5 were case reports/series, and 3 did not assess clinical efficacy. TCS clinical efficacy studies were primarily interventional non-comparative ($n = 7$ each). Other designs were utilized less often [randomized vehicle-controlled ($n = 3$), randomized active-controlled ($n = 2$ and $n = 4$, respectively), and randomized active-/vehicle-controlled ($n = 1$ each)]. Studies that included infants were more often interventional non-comparative ($n = 3$) or randomized active-controlled ($n = 3$) compared with randomized vehicle-controlled ($n = 1$). The single trial that included newborns was randomized, comparing different dosing regimens. Of the active-controlled studies, 1 was once versus twice daily treatment, 1 was proactive versus reactive treatment, 1 was soak-and-smear vs dry skin application, and 1 was application before versus after emollient, all with the same TCS. The only active- and vehicle-controlled trial compared different formulations of the same TCS. Among the 20 interventional TCS studies, 1 used lowest potency, 5 used low potency, 2 used lower-medium potency, 11 used medium potency, none used high potency, and 1 used very high potency TCS. Of these, two of the medium potency TCS studies included a low potency TCS for the face and other sensitive skin areas (Table 2). More studies of mild-to-moderate disease focused on older age groups (Table 2).

There were 59 references with TCIs as primary treatment [73–131]; an additional 5 references used TCIs as an active comparator. Of the 59 references, 9 were pooled/secondary/post hoc analyses of previously published studies and 7 studies did not assess clinical efficacy. The greatest numbers of TCI clinical efficacy studies in adolescents, children, and/or infants were interventional non-comparative ($n = 12$, $n = 16$, $n = 6$, respectively) or randomized vehicle-controlled ($n = 8$, $n = 12$, $n = 3$) compared with randomized active-controlled ($n = 9$, $n = 10$, $n = 3$). Of the active-controlled studies, 9 were versus TCS, 1 was versus the same TCI using different doing regimen, 1 was versus another TCI, and 2 were versus emollient/device cream.

The majority of references (10/16, 63%) supporting topical PDE4 inhibitors were pooled or post hoc analyses [132–147]. Of the remaining references, 3 were randomized vehicle-controlled, 2 were interventional non-comparative, and 1 was randomized active-controlled versus

	Proportion of Patents Treated											
Study Design	Topical calcineurin inhibitor	Topical corticosteroid	Systemic immunotherapy	Systemic immuno-suppressant	Topical antibiotic	Systemic corticosteroid	Systemic antibiotic	Oral antihistamine	Emollient	Phototherapy	Bathing	Dilute bleach baths
Prospective Study												
Analysis of 100 patients with AD (based on history and clinical presentation) attending the outpatient department of Dermatology of Isra University Hospital (Pakistan) [29]		NR			18%	Unclear	39%		NR			
Questionnaire-based study of 119 patients 6 months-12 years with AD (Poland) [30]	52%	77%						65% (RoA NOS)	96%			
Observational, cross-sectional study of 60 patients with AD from all age groups (majority of patients were 310 years, mean age 13.8±15.1 years) attending the dermatology outpatient department of Amrita Institute of Medical Sciences from Jan 2010-May 2010 (India) [31]	5%	75%		3%	7%	25%	20%	75%	95%	18%		
Ongoing postmarketing safety registry study of 4105 patients 2-17 years with physician-confirmed mild-to-moderate AD and being treated with pimecrolimus (PEER) (US) [32]	55-100% decreasing through 3 years of enrollment	48-56% steady through 3 years of enrollment										
Population-based, multicenter, observational, descriptive, cross-sectional epidemiologic study of 171 patients with AD (63% <15 years) with prospective data collection from patients seeking allergology consultation services in Spain [33]	31%	49%						72%	94%			
Claims Database												
Analysis of 39,526 patients with commercial healthcare insurance plan who saw a dermatologist for a primary ICD-9 diagnosis of AD 2010-2015 (US) [34]												
Males 0-19 years		57%				1%		9%				
Females 0-19 years		72%				2%		11%				

Fig. 2 Clinical practice patterns. *AD* atopic dermatitis, *ICD* international classification of diseases, *NOS* not otherwise specified, *NR* not reported, *PIM* pimecrolimus, *RoA* route of administration, *TAC* tacrolimus, *TCI* topical calcineurin inhibitor

	Proportion of Patents Treated											
Study Design	Topical calcineurin inhibitor	Topical corticosteroid	Systemic immunotherapy	Systemic immuno-suppressant	Topical antibiotic	Systemic corticosteroid	Systemic antibiotic	Oral antihistamine	Emollient	Phototherapy	Bathing	Dilute bleach baths
Population-based analysis of 11,55 patients with AD in 2003 and 2004 (Germany) [35]												
1211 patients 0-2 years	3% TAC 15% PIM	26% class 1 17% class 2 50% class 3 <1% class 4										
1949 patients 3-11 years	4% TAC 12% PIM	15% class 1 12% class 2 44% class 3 1% class 4										
1449 patients 12-17 years	5% TAC 11% PIM	9% class 1 17% class 2 47% class 3 2% class 4				4%				2%		
US Medicaid health care utilization and claims analysis of patients <20 years with TCI prescription Jan 2001-Dec 2009 (US) [36]												
57,664 new users of TAC (33.1% with AD ICD10 code)												
Patients <20 years 2001-2009		34%				12%		24%				
Patients <2 years 2001-2004	37%											
Patients <2 years 2007-2009	23%											
425,242 new users of PIM (21.0% with AD ICD-10 code)												
Patients <20 years 2001-2009		17%				9%		19%				
Patients <2 years 2001-2004	47%											
Patients <2 years 2007-2009	34%											
Retrospective Analysis												
Case-control cohort study using longitudinal electronic medical records of 1163 infants consulting general practitioners diagnosed with AD before 1 year Jan 2000-Dec 2003 followed for up to 9 years (France) [37]												
1st year of follow-up		50%			25% 'antiseptics'				50%			
2nd year of follow-up									16%			
3rd to 9th year of follow-up									4% - 8%			
Chart review of 62 children (age NOS) with AD admitted at outpatient clinic in the previous 5 years (Portugal) [38]	15%	47%	51%	5%			16%					

Fig. 2 continued

	Proportion of Patents Treated											
Study Design	Topical calcineurin inhibitor	Topical corticosteroid	Systemic immunotherapy	Systemic immuno-suppressant	Topical antibiotic	Systemic corticosteroid	Systemic antibiotic	Oral antihistamine	Emollient	Phototherapy	Bathing	Dilute bleach baths
Chart review of 218 patients (266 hospitalizations) <18 years of age hospitalized Jan 1980-Apr 2010 for intensive topical treatment for AD (US) [39]	Prior to hospitalization: 14%	Prior to hospitalization: 60%				Prior to hospitalization : 1%						
Chart review of patients <18 years of age with AD and ≥2 dermatology visits during study period (US) [40]												
303 patients 2000-2005				<1%			29%			1.3%	18%	<1%
450 patients 2009-2014				1%			63%			0%	12%	15%
Chart review of 50 patients 0-12 years diagnosed with AD (Pakistan) [41]	0%	100%										
Chart review of 500 patients (1224 prescriptions) ≤6 years seen in the allergology department and diagnosed with asthma, allergic rhinitis, and/or AD (35%) Jan 2012-Jun 2012 (Portugal) [42]	<1%							35%				
Cross-sectional study of outpatient encounters for AD compiled from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey (US) [43]												
2.8 million visits for patients 0-18 years 1997-2000		34%				17%		14% (RoA NOS)				
4.6 million visits for patients 0-18 years 2001-2004	23% (10% TAC, 13% PIM)	25%						21% (RoA NOS)				
0.7 million visits for patients 0-2 years 1997-2000		21%				6%		7% (RoA NOS)				
1.3 million visits for patients 0-2 years 2001-2004	22% (8% TAC, 14% PIM)	24%						18% (RoA NOS)				
Survey/Interview												
124 surveys completed by parents of patients with physician-diagnosed AD who had a pediatric allergy clinic visit in prior 3 years (US) [44]	5%	32%						84%	27% emollients 36% 'creams' NOS			
Telephone interviews with 2002 patients and caregivers of children (45% were patients/ caregivers of patients <18 years) with moderate-to-severe AD Jul 2004-Sep 2004 (US, France, Germany, Spain, UK, Netherlands, Mexico, Poland) [45]	9% TAC 25% PIM	65%							27%			

Fig. 2 continued

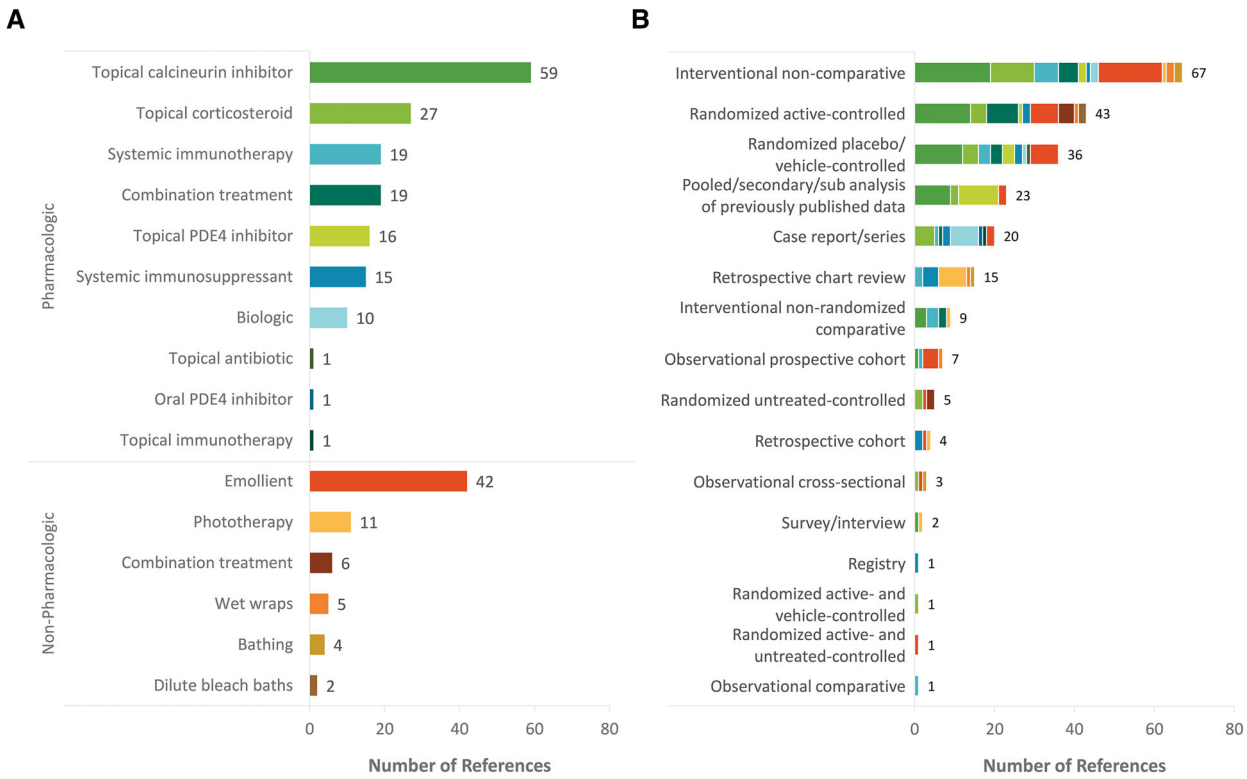

Fig. 3 Number of references by primary investigated treatment (**a**) and study design (**b**; n = 238). The same color coding used in **a** was used to indicate primary treatment investigated in **b**, and in all other figures. *PDE4* phosphodiesterase 4

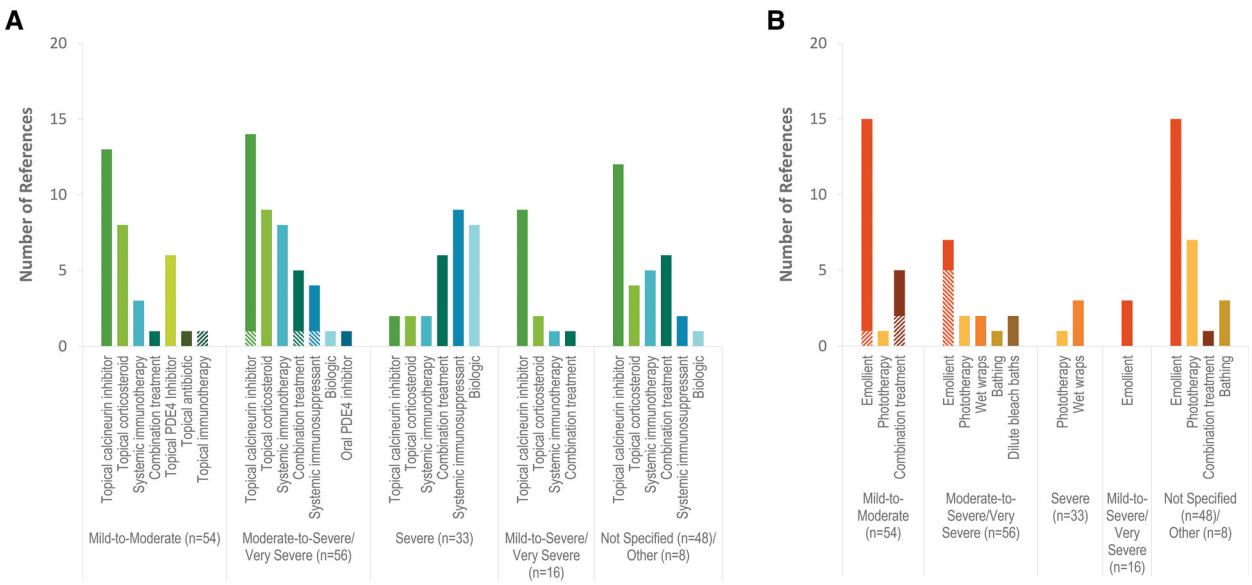

Fig. 4 Number of references investigating pharmacologic (**a**) and non-pharmacologic (**b**) treatments by AD severity (n = 215). Solid filled bars represent ranges listed on the x-axis; pattern filled bars represent the "mild" (n = 4) or "moderate" (n = 8) subset of the indicated ranges. *PDE4* phosphodiesterase 4

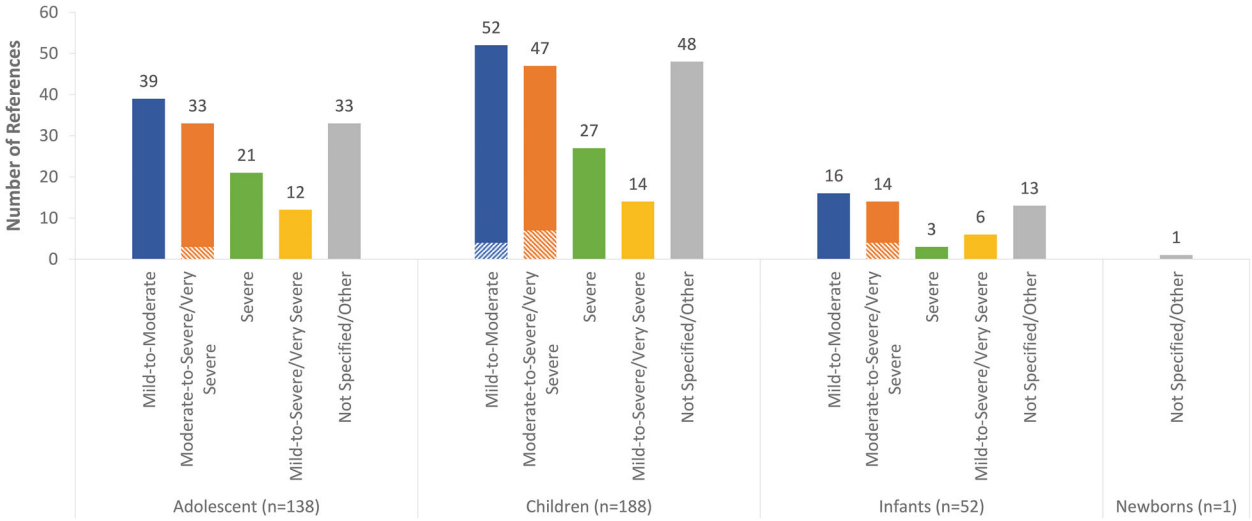

Fig. 5 Number of references by AD severity and age group (n = 215). Solid filled bars represent ranges listed on the x-axis; pattern filled bars represent the "mild" (n = 4) or "moderate" (n = 8) subset of the indicated ranges

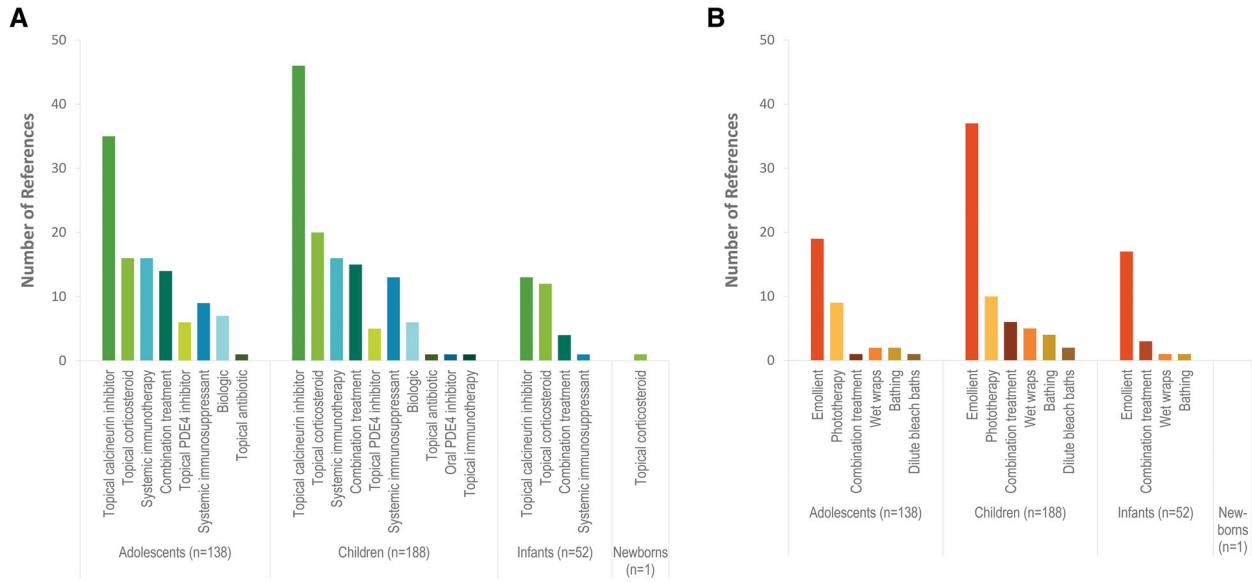

Fig. 6 Number of references investigating pharmacologic (**a**) and non-pharmacologic (**b**) treatments by age group (n = 215). *PDE4* phosphodiesterase 4

the same topical PDE4 inhibitor using a different dosing regimen.

Topical combination treatments included TCS–antibiotic (n = 4), TCI–phototherapy (n = 1), TCS–TCI (n = 6), TCS–emollient (n = 3), and TCS–wet wrap (n = 2) [148–163]. There was 1 case series. The remaining studies were interventional non-comparative (n = 3), randomized vehicle-controlled (n = 3), or randomized active-controlled (n = 9; 8 were vs monotherapy and 1 was vs emollient) and included adolescents (n = 11), children (n = 13), and infants (n = 4).

Table 2 Number of references investigating topical corticosteroids by potency, AD severity, and age group

Topical corticosteroid (TCS) potency[c]	AD severity[a]					Age group[b]			
	Mild-to-moderate	Moderate-to-severe/very severe	Mild-to-severe/very severe	Severe	Not specified/other	Adolescents	Children	Infants	Newborns
Lowest/class VII (n = 5)	1			1	3	2	2	2	
Low/class VI (n = 5)	3	2				3	5	5	
Lower–medium/class V (n = 3)	1	2				2	3	3	
Medium class III–IV (n = 6)	1	2	1	1	1	3	6	1	1
High/class II (n = 0)									
Very high/class I (n = 6)	2	3	1			6	4	1	

AD atopic dermatitis

[a] Mild-to-moderate includes 'mild' (n = 4), moderate-to-severe/very severe includes 'moderate" (n = 8)

[b] Studies that spanned more than one age group are counted more than once

[c] If a study included > 1 TCS of different potency (e.g., medium potency for the body and low potency for face), it was counted for the highest potency TCS used; lowest includes methylprednisolone aceponate 0.1% (formulation not specified), methylprednisolone aceponate 0.1% cream, prednisolone valerate 0.3% ointment, triamcinolone acetonide 0.0025% cream; low, desonide 0.05% foam, desonide 0.05% hydrogel, fluocinolone acetonide 0.01% oil; lower-medium, hydrocortisone butyrate 0.1% cream, fluticasone propionate 0.05% lotion; medium, betamethasone valerate 0.1% ointment, clobetasone butyrate 0.05% cream, clocortolone pivalate 0.1% cream, fluticasone propionate 0.005% ointment, triamcinolone acetonide 0.1% ointment; very high, clobetasol propionate 0.05% cream/lotion, fluocinonide 0.1% cream

In addition, topical antibiotic treatment was the subject of a randomized vehicle-controlled study in children and adolescents [164], and topical immunotherapy with *Streptococcus pyogenes* ointment was the topic of a case study in a child [165].

Topical pharmacologic treatments were the most frequently investigated. Overall, evidence was high level and covered a wide range of age groups. Notably, the only reference to include newborns was a TCS trial.

Systemic Pharmacologic Treatments

There were 15 references that included one or more systemic immunosuppressant agents as primary treatment [166–180]; 1 additional reference used a systemic immunosuppressant as an active comparator. Medications included azathioprine ($n = 7$), cyclosporine ($n = 6$), cyclosporine–glucosamine combination ($n = 2$), methotrexate ($n = 3$), and mycophenolate mofetil ($n = 3$). Of the 15 references, 2 were case reports/series, 6 were retrospective chart reviews/cohorts, and 1 was a registry. Of the remaining 6 studies, all assessed clinical efficacy—1 was interventional non-comparative (including children and adolescents), 2 were randomized placebo-controlled (1 in adolescents, 1 in children), 2 were randomized active-controlled (1 versus a different systemic immunosuppressant in children and 1 combination systemic immunosuppressant therapy versus monotherapy in adolescents).

There were 19 references that used systemic immunotherapy as primary treatment [181–199] including subcutaneous ($n = 12$), sublingual ($n = 4$), or oral antigen administration ($n = 1$), and intradermal ($n = 1$) or subcutaneous *Mycobacterium vaccae* ($n = 1$). Of these, 1 was a case report and 2 were retrospective chart reviews. Of the remaining 16 studies, 15 assessed clinical efficacy. Of these, 6 were interventional non-comparative (1 in adolescents, 1 in children, 4 included both groups), 3 were randomized placebo-controlled (1 in adolescents, 1 in children, 1 included both groups), 4 were untreated-controlled (all included children and adolescents), and 2 were active-controlled (1 in adolescents, 1 included both groups). Of the active controlled trials, both were versus conventional multimodal therapy. There were no immunotherapy trials in infants or newborns.

There were 10 references that included omalizumab ($n = 9$) or ustekinumab ($n = 1$) biologic treatment [200–209]. Of these, only 3 were interventional: 2 non-comparative (1 in adolescents, 1 in children and adolescents) and 1 randomized placebo-controlled in children and adolescents. The other 7 were case reports/series.

Systemic combination treatments included immunotherapy–immunomodulator ($n = 3$) and immunotherapy–immunosuppressant ($n = 1$) combinations [210–213]. They were interventional non-comparative ($n = 2$) and interventional non-randomized comparative ($n = 2$) and included children and adolescents ($n = 3$) or adolescents alone ($n = 1$).

In addition, there was a case report of oral PDE4 inhibitor treatment in a child [214].

Systemic treatments were investigated less frequently than topical treatments. The level of evidence in these references was lower than those in references about topical treatments. There was only 1 paper among 60 that included infants; none included newborns.

Non-pharmacologic Management

There were 53 references addressing first-line skin care as primary treatment [215–267], including 42 papers assessing emollients (an additional 4 used emollient as an active comparator), 4 assessing bathing (an additional 2 references used bathing as an active comparator), 2 assessing dilute bleach baths, and 5 assessing emollient–cleanser combinations. Of these 53 references, 2 were case reports/series and 2 were pooled/secondary/subgroup analyses of previously published data. All but one of the remaining papers assessed efficacy including 2 retrospective chart reviews/cohorts, 6 observational studies, 17 interventional non-comparative studies, 10 randomized untreated/vehicle-controlled studies, 12 randomized active-controlled studies, and 1 randomized active- and untreated-controlled study. Of the trials that included an active comparator, 2 were versus TCS, 5 were versus a different emollient, 2 were versus bathing, and 3 were versus

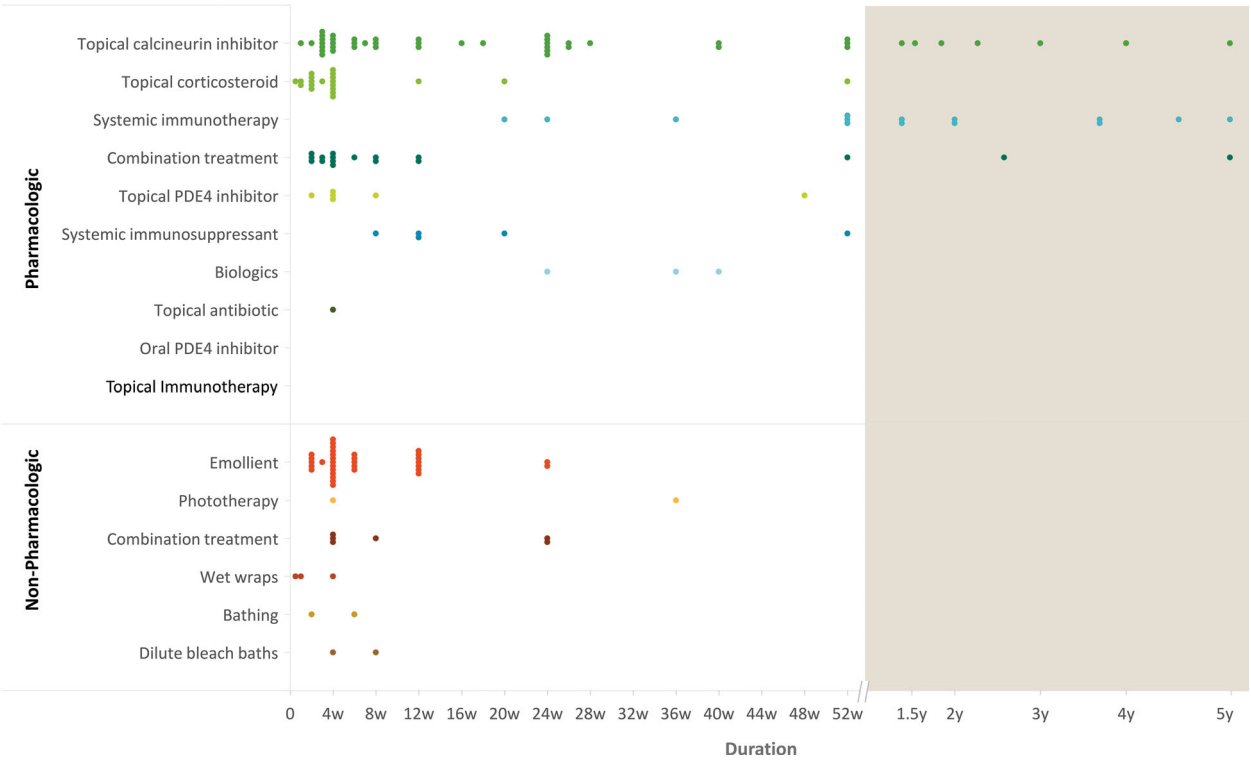

Fig. 7 Duration of treatment for short-acting treatments/duration of follow-up for long-acting treatments in interventional studies (n = 162). Duration of treatment/follow-up could not be determined for 1 study published as an abstract. *PDE4* phosphodiesterase 4, *w* weeks, *y* years

monotherapy. First-line skin care efficacy studies primarily included children (n = 48).

A total of 5 references assessed wet wrap therapy as primary treatment [268–272]. Of these 1 was a retrospective chart review, 1 was an observational prospective cohort, and 2 were interventional non-comparative. The remaining reference was a randomized active-controlled study versus conventional treatment in children and infants.

There were 11 references assessing phototherapy as primary treatment [273–283]. The majority (7/11, 64%) were retrospective chart reviews. One additional reference included phototherapy as an active comparator.

Emollients were the second most investigated treatment. Overall, published studies of non-pharmacologic treatments included all age groups, except newborns. References investigating emollients and other skin care included high level evidence, while references investigating wet wrap therapy and phototherapy had lower level evidence.

Treatments and Interventional Trial Evidence by Duration of Treatment

Out of the 162 interventional studies, 106 (65%) were less than 12 weeks in duration (Fig. 7). Only TCIs, TCS, systemic immunotherapy, and pharmacologic combination treatment have been investigated for more than 52 weeks (Fig. 7). All TCS and TCI studies that were 24 weeks or longer used intermittent (less than daily treatment) or proactive (treating at first signs or symptoms of a flare) treatment (Fig. 7).

DISCUSSION

The results of our analysis largely reflect current AD treatment guidelines [1, 16–21], and the quality of evidence supporting the use of these treatments is high (including randomized controlled trials). The relatively large number of references investigating emollient treatment and the high prevalence of emollient use reported in clinical practice (up to 96%; Fig. 2) are indirect indicators that first-line management recommendations are being widely implemented.

The highest proportion of published literature in this analysis focused on the use of TCIs, likely reflecting the search interval. Topical tacrolimus was approved by the FDA in 2000, and pimecrolimus in 2001, 3 years prior to the search start date. One year into the search interval, substantial controversy focused on the theoretical risk of TCI-related lymphoma and a Boxed Warning. The number of references supporting the use of TCS is smaller than expected and more focused on mild-to-moderate disease and older age groups (Fig. 3). This may also be related to the search interval, beginning decades after widespread, "grandfathered" use of these medications. It could also reflect comparatively limited funding for clinical research to study older, generic drugs, or changes in treatment patterns over time [284].

The potencies of TCS and durations of treatment used in clinical trials reflect guideline recommendations to use the lowest potency agent for the shortest time period that will control symptoms, but long-term studies of TCS are lacking. Published studies of TCIs focus more on the safety and efficacy of monotherapy than as guidelines-directed long-term maintenance, but include data on intermittent use for up to 5 years [119, 285].

Current guidelines also recommend other options for moderate-to-severe AD including wet wrap therapy (with or without TCS), phototherapy, or systemic immunosuppressants (cyclosporine, azathioprine, or methotrexate, with mycophenolate mofetil as an alternative). These recommendations are also reflected in reports of clinical practice and the medical literature, although the number of references identified and level of evidence in those references are low (Fig. 3). This is not unexpected as these treatments are associated with safety concerns and limited to use in a subset of patients with severe AD. However, the high impact of severe AD represents a significant unmet need that deserves additional study.

Systemic antimicrobials, topical antibiotics, and other antiseptic measures are discussed but not recommended by the guidelines, except for oral antivirals/antibiotics and dilute bleach baths in patients with AD who have clinical signs of secondary infection. For patients who experience frequent bacterial infections, guidelines suggest that dilute bleach baths be considered as a maintenance treatment. The range of systemic antibiotic use among reports of clinical practice was wide (16–63%; Fig. 2). This likely reflects the lack of well-accepted clinical and laboratory biomarkers to define infection, rather than colonization, as well as the short-term improvement commonly observed after treatment with systemic anti-staphylococcal antibiotics [286]. However, high-level evidence supporting the use of systemic antibiotics is lacking, and a small meta-analysis recommends against this treatment [286].

Guidelines also suggest that sedating oral antihistamines may be useful, especially in the context of interrupted sleep. Like use of systemic antibiotics, the range of published practice patterns is wide (7–84%; Fig. 2), possibly reflecting lack of evidence and potential adverse effects [287].

The AAD guidelines recommend avoiding systemic corticosteroids for AD, while the AAAAI/American College of Allergy, Asthma, and Immunology (ACAAI), and European guidelines caution against their use, especially on a long-term basis. In accordance with these guidelines, our search strategy did not identify any studies that specifically investigated the use of systemic corticosteroids, although surprisingly their use ranged from 1–25% in reports of clinical practice (Fig. 2).

Several references focused on the use of systemic immunotherapy, many of which use higher level interventional evidence. The AAD guidelines do not recommend allergen-specific immunother-

apy because of insufficient evidence, while the AAAAI/ACAAI and European guidelines suggest that it can be useful in selected patients.

Biologic therapy is discussed but not recommended by any current guideline because of insufficient evidence. There were a few references regarding use of biologic agents in pediatric patients, with only one reporting higher level evidence.

Regarding patient age groups and AD severity, there was only one reference on AD treatment in newborns and few references with high quality evidence to support treatment of severe AD using systemic agents. Although recent publications have investigated the role of emollients in preventing atopic dermatitis in newborns, they did not meet the inclusion criteria for this systematic review and were not included in this analysis [288, 289].

We and others [290] have found that the definitions of mild, moderate, and severe used in clinical trials often overlap and many trials use a range of severity (i.e., mild-to-moderate or moderate-to-severe). This lack of standardization precludes comparative effectiveness analysis of available data. There is a general need for a better definition of AD severity to guide clinical use. For example, topical tacrolimus is FDA-approved for moderate-to-severe AD [291]; however, severe AD often requires systemic therapy.

There is also a striking lack of medical literature for long-term use of many of the treatments included in this analysis. The only topical treatment that has been studied for longer than 1 year is TCI and the only systemic treatment is immunotherapy, which is not recommended by current guidelines for routine treatment. Given the chronic nature of AD and the need for ongoing maintenance treatment, long-term data is critical for making sound treatment decisions, especially for pediatric patients who are more susceptible to developmental effects and systemic exposure to topical treatments.

This scoping review expands on the results of a recent related publication; Nankervis et al. [292] assessed the quality of systematic reviews and randomized controlled trials for AD treatments in patients of all ages. Our analysis included additional primary data sources (abstracts, chart reviews, case reports, and other non-randomized data) because in the absence of high level evidence in pediatric patients, dermatologists often rely on these primary data sources when making clinical decisions regarding their patients. Including this diversity of publication types reflects "real-world" clinical practice, but limits our ability to assess the quality and outcomes of the references included in this analysis. However, the lack of a central database of conference abstracts precludes inclusion of data from all possibly relevant meetings, and some important meetings may have been inadvertently overlooked in our search.

CONCLUSIONS

In summary, treatments investigated in published medical literature include those recommended in current treatment guidelines; however, clinical practice pattern publications include a scope of therapies not supported by high level evidence or current treatment guidelines. This may be related to the fact that clinical practice patterns are often not completely evidence-based, but driven by medical training, individual experience, and institutional "norms". This makes change difficult and also delays and interferes with introduction of innovative treatments into guidelines and practice [293]. Finally, standardized data are needed to support the treatments that are actually used in clinical practice, especially those used in younger children and for long-term treatment and severe disease.

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