

Guidelines for the management of atopic dermatitis in children: A systematic review of the literature and quality appraisal with AGREE II

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May 10, 2022

Abstract

Background: Numerous guidelines have been published for atopic dermatitis management in children in recent years. To date, the quality of the newest guidelines has not been appraised. **Objective:** To identify and evaluate guidelines for the management of atopic dermatitis in children. **Design:** A review of the guidelines for the management of atopic dermatitis in children and quality appraisal with AGREE II was conducted. **Methods:** We reviewed literature retrieved from PubMed, Web of Science, Ovid, ScienceDirect, Embase, China National Knowledge Infrastructure, WanFang Data, and guidelines websites. Search period from 1 January 2016 to 31 December 2021. The following keywords were used for searching: ‘atopic dermatitis’, ‘atopic eczema’, ‘eczema’, ‘guideline’ and ‘consensus’. The quality of the guidelines was assessed by two assessors using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument independently, and domain scores were considered of sufficient quality when > 60%. Guidelines recommendations were reviewed. **Results:** Nineteen guidelines were included in the study. Three guidelines were graded A level that recommended for use in practice. Eleven guidelines were graded B level that recommended for use in revision. The remaining five guidelines were rated C level not as recommended. The average score of six domains of AGREE II was 64.76%, 48.53%, 42.35%, 73.83%, 32.23% and 70.17%, respectively. The consistency test showed that ICC ranged from 0.497 (95%CI: 0.105, 0.705) to 0.970 (95%CI: 0.93, 0.987) in the results of two assessors’ tests of the guidelines. **Conclusions:** Most guidelines were recommended for use with revision in the study. No major changes in primary management of atopic dermatitis in children compared to previous evidence. New biologic agents and complementary alternative medicine were increasingly available, but evidence for the treatment of atopic dermatitis in children was still limited.

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Word count: 2591

Article type: systematic review

Conflicts of interest

Authors have no conflicts of interest.

Financial support

This research did not receive any financial support.

Abstract and keywords

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Keywords: Dermatitis, Atopic; Eczema; Child; Guideline

Key message

The quality of available guidelines for the management of Atopic Dermatitis in children varies.

Basic care for Atopic Dermatitis in children is not changed much. Emerging therapies need more evidence to support effectiveness and safety in children.

Main text

Background

Atopic dermatitis (AD) also called atopic eczema, eczema, is a common chronic, inflammatory skin disease.^{1,2} It is characterized by pruritus, dryness, and inflammation. The chronic course of the disease and recurrent episodes impose a severe physical and mental burden on patients and their families. The incidence of AD is 10~20% in children and 5% in adults.³⁻⁵ AD usually begins in childhood with 90% of patients having an

onset before age five.⁶ The occurrence of AD is mainly related to genetics, immune function, skin barrier function, some allergen triggers such as dust mites, pollen, food, synthetic fibers, woolens, sweat, sunshine, and infections, etc. In addition, non-immune factors such as stress, anxiety and other negative emotions can also aggravate AD.⁷⁻¹⁴ The diagnosis of AD is based on the clinical history and skin symptoms, other tests such as patch testing and food challenge test are also used.^{15,16} The worldwide diagnosis criteria are Williams Diagnostic Criteria from the UK and Hanifin-Rajka Diagnostic Criteria.^{17,18}

The incidence of AD has been on the rise worldwide in recent years, and the treatment of AD has received continuous attention, with different countries and organizations issuing a series of guidelines and consensus recommendations on the management of AD.¹⁹ Although there are differences in treatment concepts and approaches to the management of AD for many factors such as different regions, dietary structures and cultural backgrounds. Therefore, it is necessary to evaluate and review the current guidelines to apply high-quality evidence available.

The objectives of this study were (a) to evaluate the existing guideline evidence for the management of AD in children, and (b) to evaluate the similarities and inconsistencies in recommendations of guidelines for the management of AD in children.

Methods

Inclusion criteria

(a) clinical practice guidelines (CPG) or expert consensus-based guidelines for the management of atopic dermatitis published, (b) guidelines apply to a population that includes children, (c) guidelines were published after January 1, 2016, (d) language is Chinese or English, (e) included guidelines are the latest version of the guidelines.

Exclusion criteria

(a) expert consensus only, (b) applicable to adults only, (c) older version of the same guideline, and (d) inability to access the full text of the guideline.

Search strategy

A systematic search of related databases, including (a) Guidelines databases: guide.medlive.cn, National Institute for Health and Clinical Excellence (NICE), National Guideline Clearinghouse (NGC), Scottish Intercollegiate Guidelines Network (SIGN), Registered Nurse' Association of Ontario (RNAO), World Health Organization (WHO), Joanna Briggs Institute (JBI), Guidelines International Network (GIN), (b) clinical database: PubMed, Embase, Web of Science, CNKI, WanFang Data. The search period was from 1 January 2016 to 31 December 2021. The search method was a combination of subject terms plus free terms. English and Chinese search terms included atopic dermatitis, atopic eczema, eczema, guideline, consensus, etc.

Literature selection and data extraction

Two researchers independently searched the literature, screened and collected data according to the inclusion and exclusion criteria. In case of disagreement, consult the third researcher. After computerized de-duplication using the literature management software, investigators read the title and abstract alone for initial screening, and then obtained the full text for re-screening, and extracted: basic information such as country, year, and organization of publication, information related to guideline quality evaluation and guideline recommendations for content analysis, etc.

Quality appraisal and consistency test

The quality of included guidelines was evaluated by two investigators using AGREE II instrument, with the assistance of the third investigator in case of disagreement. AGREE II is currently the most widely used and extensive tool for evaluating guidelines.²⁰ 23 items are evaluated in six domains of Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, Editorial Independence, and two overall evaluations items. Each item is graded on a seven-point scale, one point means

strongly disagree, and seven-point means strongly agree, one to seven points are given based on whether the guidelines report meets the criteria or conditions for the entry, and the distribution of points depends on the completeness and quality of the report. After completing the evaluation of each entry, the quality score of each domain was calculated separately, calculated as = (actual score for the domain - lowest possible score) / (highest possible score - lowest possible score) × 100%, which means the higher the standardized percentage score for each domain, the higher the quality of the guideline. Guidelines are rated based on standardized percentage scores in six domains, and if the total standardized score of each field is [?] 60%, it is recommended for the A level. If the number of fields with standardized total scores is [?] 30% over 3, but there are fields with scores < 60%, it is recommended for B level. If the number of fields with a standardized total score < 30% over 3 is recommended for the C level.

ICC was used for the consistency test according to the results of the evaluation according to the researcher's guidelines. ICC [?] 0.75 indicated high consistency.

Results

Guidelines characteristics

A total of 367 kinds of literature were searched from databases and guideline websites including six Chinese version guidelines. After duplicate checking, 312 literatures were screened and nineteen guidelines were finally included. PRISMA flow diagram was shown in Figure 1. Of the included guidelines, seventeen were in English and two were in Chinese. Thirteen were CPGs and six were expert consensus-based guidelines, all of which were intended for children. The basic characteristics of the included guidelines are shown in Table 1.²¹⁻⁴⁰

AGREE II scores

Three guidelines from Europe, Japan, and Malaysia^{25-27,30} were rated A level in the overall evaluation and recommended for use in practice. Eleven guidelines were rated B level and recommended for use after revision.^{21-24,28,29,34-36,38,40} Five guidelines were rated C level and not recommended for use.^{31-33,37,39} The specific results of the criteria percentage scores for each domain of the quality evaluation of the included guidelines are shown in Table 2.

Scope and Purpose

There were three items and the mean score for the scope and purpose domain was 64.76% (range 5.55%~100%). Most guidelines clearly described their overall aims, the specific health questions and target populations. The Chinese Consensus-based guideline³⁹ had the lowest score.

Stakeholder Involvement

This domain focused on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users. The mean score was 48.53% (range 5.55%~91.66%). Neither the Italian³³ nor the Chinese consensus-based guidelines³⁹ explicitly stated whether the guideline construction groups included all relevant professionals and whether the views and wishes of the target population were collected.

Rigor of Development

Rigor of Development relates to the process used to gather and synthesize the evidence, and the methods to formulate and update the recommendations. The average score was 42.35% (range from 3.57%~91.66%). Only four guidelines^{25-28,30} scored > 60%.

Clarity of Presentation

Clarity of Presentation deals with the guideline's language, structure, and format. The average score was 73.83% (range from 8.33%~97.22%) which was higher than other domains' average scores. Four guidelines^{31,32,37,39} scored < 60%.

Applicability

Applicability pertains to the possible barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline. The average score of applicability was 32.23% (range from 2.08%~77.08%) which was the lowest average score domain. Only four guidelines^{25-28,30} scored > 60%.

Editorial Independence

Editorial independence involves the formulation of recommendations without undue bias towards competing interests. The average score of editorial independence was 70.17% (range from 0~100%). Two Chinese expert consensus-based guidelines^{37,39} scored < 30%.

Consistency Test

The results showed that the *ICC* ranged from 0.497 to 0.970, indicating good consistency in the results of the investigators' appraisal of the guidelines, as shown in Table 2.

Management of atopic dermatitis in children

The nineteen guidelines included in the study were analyzed for content related to the management of atopic dermatitis in children, and the main content keywords involved are shown in Table 3. The management and treatment measures for AD are summarized in a total of 23 entries from 8 parts, including severity assessment, skin care, topical medication treatment, systemic medication treatment, non-pharmacological treatment, adjuvant therapy, patient education, and complementary medicine. Details are shown in Table 4.

Discussion

A total of nineteen guidelines for the management of AD in children were included in the study, thirteen of which were CPG and two guidelines were in Chinese. The quality of the included guidelines was evaluated by the AGREE II instrument, and three guidelines were rated A level and eleven were rated B level, which was of high overall quality. Those who received a C-level quality rating were mainly evidence-based expert consensus.

More research has been focused on AD worldwide with the development and advancement of medicine, but it seems that the main treatment of AD has not changed so much. AD occurs predominantly in infancy and early childhood, symptoms are predominantly mild, with a few cases extending into adulthood.^{41,42} All guidelines suggest that for mild, non-episodic AD without other infections, the primary concern is basic skin care, such as keeping skin moist and clean. Skin moisturization and cleansing can reduce the severity of AD and the frequency of medication use.⁴³ The choice of moisturizer can be based on patient preferences. There is no consensus on the dosage, frequency and timing of application, but most guidelines recommend choosing the dosage based on fingertip units (FTU), and European guideline suggests specific dosages (shown in Table 5). Also, it is recommended to use it together with medication to reduce the side effects when it comes to flares. Skin cleansing is as important as moisturizing. The use of a moisturizer immediately after the end of daily bathing was agreed upon for this recommendation across guidelines. There is no agreement on the time and temperature of bathing water, most recommend 5 to 10 min and a water temperature of 27 to 40, water temperature too high can cause itching of the skin.⁴⁴ Cleaners refer to patient preferences and try to use neutral or low pH, non-allergenic substances or additives.

This study included AD guidelines published after 2016, and it can be seen that the initial reports on the use of biologics were small sample size studies, and their safety and efficacy could not be confirmed especially in children, who are at high risk of AD and are more cautious about the use of biologics. Dupilumab is the first biologic agent for adult AD approved in Europe and FDA in 2017.^{45,46} Dupilumab is a fully human monoclonal antibody that blocks the common α -chain of the receptor for interleukin-4 and interleukin-13 that shows positive control of the extent of AD lesions and pruritus symptoms. Dupilumab was approved in South Korea in 2018 and China in 2020 for use in adults with moderate to severe AD, respectively. With increased relevant evidence, Dupilumab was approved by FDA in 2019 for adolescent patients aged

12~17 years and in 2020 for pediatrics aged 6~11 years with moderate-to-severe AD. Other biologics such as omalizumab, Ustekinumab, rituximab, mepolizumab, Nemolizumab, and alefacept are not recommended in the guidelines for now due to the limited evidence available. Cost-effectiveness also needs to be considered when using biologics for AD in children.⁴⁷

Traditional medicine such as Chinese herbal medicine, acupuncture, massage, homeopathy, and aromatherapy, are widely used in some Asian countries. However, the safety and efficiency of traditional medicine are still waiting to be verified. For example, the use of herbal medicine may cause metal element poisoning and increase the nephrotoxicity of patients.⁴⁸ Therefore, most existing guidelines do not recommend conventional medicine for the treatment of AD, and more research evidence is needed for its application in children. It is noteworthy that 67.4% of AD patients in a survey conducted in Hiroshima, Japan, used herbal medicine. In a questionnaire survey of guardians of children with AD at their first visit in Tokyo, patients with steroid phobia used traditional medicine more frequently than patients without steroid phobia (22.2% vs. 13.0%, $P=0.013$).^{27,49} China has published guidelines for Chinese medicine to AD which to guide clinical practitioners in the application of Chinese herbal medicines in 2021, which is currently only available in Chinese and mentions limited evidence of effectiveness, and more clinical studies are needed to confirm the efficacy of these herbal medicines in the future.

In addition to traditional medicine, there are several complementary treatments like dietary restrictions, essential fatty acids, vitamin D, probiotics and allergen immunotherapy, etc. Above all, dietary restrictions are not recommended especially for children, pregnant and lactating women. Unless patients have a clear allergy to food or a positive oral irritation test. Dietary restrictions can cause malnutrition, which is difficult to implement in real life and reduces the quality of life. Patients and family members must be informed of the pros and cons of this method before implementation. Secondly, certain agents such as essential fatty acids, vitamin D, and probiotics are not recommended due to insufficient evidence available. In particular, probiotics have been shown to have no significant effects in pediatrics patients with AD. For allergen immunotherapy, it can be considered in moderate to severe AD with a combination of allergic rhinitis, asthma, dust mite, and pollen allergy, otherwise it is not recommended. However, these conclusions may also be overturned later.

Almost all guidelines have mentioned patient education. Patient education has been proven to reduce disease severity, improve quality of life and improve mental health. Although patient education has never been neglected, it still seems to be ineffective and steroid phobia has not diminished over time. Patient education is an ongoing, time-consuming, and high-volume effort that requires multidisciplinary staff collaboration and includes pediatricians, dermatologists, pharmacists, nursing staff, community workers, etc. There are different forms of patient education in different national backgrounds. Specialized outpatient clinics, brochures, inpatient lectures, online videos and dedicated websites are the main modes of patient education. Some developed countries from Europe carried out eczema action plans and eczema schools, which may benefit from national policy support. The implementation of patient education should take into account the applicability and cost-effectiveness of the region where it is carried out. The target of education is not only patients, but also family members, especially parents of children, to increase patient compliance and ensure the quality of life. Also, it is important to know that patients and families learn to use some self-assessment tools such as POEM so that they can be informed of the degree of control timely. In the future, there is still a need to explore more methods of education that can be satisfied by patients, families and staff to improve compliance with AD treatment.

Limitations

Our review has several limitations. First, this research was limited to the published and web-accessible literature. Second, our literature review includes articles in English and Chinese, it is possible that articles in other languages could supplement the evidence. Finally, the researchers set up keyword searches, so different researchers may use different sets of search terms, leading to different articles being analyzed.

However, considering the relatively large number of studies on AD, it is unlikely that the results will differ significantly.

Conclusions

The increasing prevalence of atopic dermatitis has coincided with an increasing number of new treatments. In this study, we conducted a content analysis of clinical practice guidelines related to the management of atopic dermatitis in the past 6 years and summarized the main points of management of this disease and the similarities and differences of recommendations in the guidelines, which provide a reference for the development of clinical practice activities and the update of clinical guidelines. More clinical evidence is needed in the future to prove the efficacy of relevant treatments for children.

Acknowledgments

None.

References

1. Thormann K, Aubert H, Barbarot S, et al. Position statement on the role of nurses in therapeutic patient education in atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2021;35(11):2143-2148. doi:10.1111/jdv.17487
2. Mohan GC, Lio PA. Comparison of Dermatology and Allergy Guidelines for Atopic Dermatitis Management. *JAMA Dermatol.* 2015;151(9):1009-1013. doi:10.1001/jamadermatol.2015.0250
3. Siegels D, Heratizadeh A, Abraham S, et al. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. *Allergy.* 2021;76(4):1053-1076. doi:10.1111/all.14631
4. Young TK, Glick AF, Yin HS, et al. Management of Pediatric Atopic Dermatitis by Primary Care Providers: A Systematic Review. *Acad Pediatr.* 2021;21(8):1318-1327. doi:10.1016/j.acap.2021.07.008
5. Patruno C, Amerio P, Chiricozzi A, et al. Optimizing a clinical guidance for diagnosis of atopic dermatitis in adults: joint recommendations of the Italian Society of Dermatology and Venereology (SIDEmaST), Italian Association of Hospital Dermatologists (ADOI), and Italian Society of Allergological, Occupational and Environmental Dermatology (SIDAPA). *G Ital Dermatol Venereol.* 2020;155(1):1-7. doi:10.23736/S0392-0488.19.06522-2
6. de Maria Diaz Granados L, Quijano MA, Ramirez PA, Aguirre N, Sanclemente G. Quality assessment of atopic dermatitis clinical practice guidelines in [?] 18 years. *Arch Dermatol Res.* 2018;310(1):29-37. doi:10.1007/s00403-017-1791-7
7. Mao W, Mao J, Zhang J, Wang L, Cao D, Qu Y. Atopic eczema: a disease modulated by gene and environment. *Front Biosci (Landmark Ed).* 2014;19(4):707-717. Published 2014 Jan 1. doi:10.2741/4237
8. Kim JE, Kim JS, Cho DH, Park HJ. Molecular Mechanisms of Cutaneous Inflammatory Disorder: Atopic Dermatitis. *Int J Mol Sci.* 2016;17(8):1234. Published 2016 Jul 30. doi:10.3390/ijms17081234
9. Danso MO, van Drongelen V, Mulder A, et al. TNF- α and Th2 cytokines induce atopic dermatitis-like features on epidermal differentiation proteins and stratum corneum lipids in human skin equivalents. *J Invest Dermatol.* 2014;134(7):1941-1950. doi:10.1038/jid.2014.83
10. Czarnowicki T, Esaki H, Gonzalez J, et al. Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)(+) TH2/TH1 cell imbalance, whereas adults acquire CLA(+) TH22/TC22 cell subsets. *J Allergy Clin Immunol.* 2015;136(4):941-951.e3. doi:10.1016/j.jaci.2015.05.049
11. Bieber T. Atopic dermatitis. *N Engl J Med.* 2008;358(14):1483-1494. doi:10.1056/NEJMra074081
12. Lack G. Clinical practice. Food allergy. *N Engl J Med.* 2008;359(12):1252-1260. doi:10.1056/NEJMcip0800871

13. De Benedetto A, Agnihotri R, McGirt LY, Bankova LG, Beck LA. Atopic dermatitis: a disease caused by innate immune defects?. *J Invest Dermatol.* 2009;129(1):14-30. doi:10.1038/jid.2008.259
14. Niebuhr M, Werfel T. Innate immunity, allergy and atopic dermatitis. *Curr Opin Allergy Clin Immunol.* 2010;10(5):463-468. doi:10.1097/ACI.0b013e32833e3163
15. Narla S, Silverberg JI. Dermatology for the internist: optimal diagnosis and management of atopic dermatitis. *Ann Med.* 2021;53(1):2165-2177. doi:10.1080/07853890.2021.2004322
16. Nuttall TJ, Marsella R, Rosenbaum MR, Gonzales AJ, Fadok VA. Update on pathogenesis, diagnosis, and treatment of atopic dermatitis in dogs. *J Am Vet Med Assoc.* 2019;254(11):1291-1300. doi:10.2460/javma.254.11.1291
17. Akan A, Dibek-Mısırhoğlu E, Civelek E, Vezir E, Kocabaş CN. Diagnosis of atopic dermatitis in children: comparison of the Hanifin-Rajka and the United Kingdom Working Party criteria. *Allergol Immunopathol (Madr).* 2020;48(2):175-181. doi:10.1016/j.aller.2019.07.008
18. Vakharia PP, Chopra R, Silverberg JI. Systematic Review of Diagnostic Criteria Used in Atopic Dermatitis Randomized Controlled Trials. *Am J Clin Dermatol.* 2018;19(1):15-22. doi:10.1007/s40257-017-0299-4
19. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis [published correction appears in *Lancet.* 2020 Sep 12;396(10253):758]. *Lancet.* 2020;396(10247):345-360. doi:10.1016/S0140-6736(20)31286-1
20. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ.* 2010;182(18):E839-E842. doi:10.1503/cmaj.090449
21. Werfel T, Heratizadeh A, Aberer W, et al. S2k guideline on diagnosis and treatment of atopic dermatitis—short version. *J Dtsch Dermatol Ges.* 2016;14(1):92-106. doi:10.1111/ddg.12871
22. Galli E, Neri I, Ricci G, et al. Consensus Conference on Clinical Management of pediatric Atopic Dermatitis. *Ital J Pediatr.* 2016;42:26. Published 2016 Mar 2. doi:10.1186/s13052-016-0229-8
23. Wong ITY, Tsuyuki RT, Cresswell-Melville A, Doiron P, Drucker AM. Guidelines for the management of atopic dermatitis (eczema) for pharmacists. *Can Pharm J (Ott).* 2017;150(5):285-297. Published 2017 May 30. doi:10.1177/1715163517710958
24. Boguniewicz M, Alexis AF, Beck LA, et al. Expert Perspectives on Management of Moderate-to-Severe Atopic Dermatitis: A Multidisciplinary Consensus Addressing Current and Emerging Therapies. *J Allergy Clin Immunol Pract.* 2017;5(6):1519-1531. doi:10.1016/j.jaip.2017.08.005
25. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I [published correction appears in *J Eur Acad Dermatol Venereol.* 2019 Jul;33(7):1436]. *J Eur Acad Dermatol Venereol.* 2018;32(5):657-682. doi:10.1111/jdv.14891
26. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol.* 2018;32(6):850-878. doi:10.1111/jdv.14888
27. Katoh N, Ohya Y, Ikeda M, et al. Clinical practice guidelines for the management of atopic dermatitis 2018. *J Dermatol.* 2019;46(12):1053-1101. doi:10.1111/1346-8138.15090
28. Chow S, Seow CS, Dizon MV, et al. A clinician's reference guide for the management of atopic dermatitis in Asians. *Asia Pac Allergy.* 2018;8(4):e41. Published 2018 Oct 29. doi:10.5415/apallergy.2018.8.e41
29. Kent KA, Clark CA. Skin Deep: Simplifying Practice Guidelines for Children With Atopic Dermatitis. *J Pediatr Health Care.* 2018;32(5):507-514. doi:10.1016/j.pedhc.2018.06.001
30. Malaysian Health Technology Assessment Section (MaHTAS). Management of atopic eczema. 2018;http://www.dermatology.org.my/pdf/CPG_Management_of_Atopic_Eczema.pdf.

31. Aoki V, Lorenzini D, Orfali RL, et al. Consensus on the therapeutic management of atopic dermatitis - Brazilian Society of Dermatology. *An Bras Dermatol*. 2019;94(2 Suppl 1):67-75. doi:10.1590/abd1806-4841.2019940210
32. Damiani G, Calzavara-Pinton P, Stingeni L, et al. Italian guidelines for therapy of atopic dermatitis- Adapted from consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) [published correction appears in *Dermatol Ther*. 2021 Sep;34(5):e15091]. *Dermatol Ther*. 2019;32(6):e13121. doi:10.1111/dth.13121
33. Chiricozzi A, Belloni Fortina A, Galli E, et al. Current therapeutic paradigm in pediatric atopic dermatitis: Practical guidance from a national expert panel. *Allergol Immunopathol (Madr)*. 2019;47(2):194-206. doi:10.1016/j.aller.2018.06.008
34. Rajagopalan M, De A, Godse K, et al. Guidelines on Management of Atopic Dermatitis in India: An Evidence-Based Review and an Expert Consensus. *Indian J Dermatol*. 2019;64(3):166-181. doi:10.4103/ijid.IJD_683_18
35. Katoh N, Ohya Y, Ikeda M, et al. Japanese guidelines for atopic dermatitis 2020. *Allergol Int*. 2020;69(3):356-369. doi:10.1016/j.alit.2020.02.006
36. Chan TC, Wu NL, Wong LS, et al. Taiwanese Dermatological Association consensus for the management of atopic dermatitis: A 2020 update. *J Formos Med Assoc*. 2021;120(1 Pt 2):429-442. doi:10.1016/j.jfma.2020.06.008
37. Atopic Dermatitis Working Group, Immunology Group, Chinese Society of Dermatology. Chinese guideline for diagnosis and treatment of atopic dermatitis (2020). *Chinese Journal of Dermatology*. 2020;53(2), 81-88.
38. Lee JH, Kim JE, Park GH, et al. Consensus Update for Systemic Treatment of Atopic Dermatitis. *Ann Dermatol*. 2021;33(6):497-514. doi:10.5021/ad.2021.33.6.497
39. Standardization project group of Clinical Application Guide for Dominant Diseases of Chinese Patent Medicine Treatment. International Clinical Practice Guidelines in Traditional Chinese Medicine: Atopic Dermatitis. *Chinese Journal of Integrated Traditional and Western Medicine*. 2020;41(2), 133-142.
40. Kulthanan K, Tuchinda P, Nitiyarom R, et al. Clinical practice guidelines for the diagnosis and management of atopic dermatitis. *Asian Pac J Allergy Immunol*. 2021;39(3):145-155. doi:10.12932/AP-010221-1050
41. Weil C, Sugerman PB, Chodick G, et al. Epidemiology and Economic Burden of Atopic Dermatitis: Real-World Retrospective Data from a Large Nationwide Israeli Healthcare Provider Database [published online ahead of print, 2022 Mar 29]. *Adv Ther*. 2022;10.1007/s12325-022-02120-6. doi:10.1007/s12325-022-02120-6
42. Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies. *Allergy*. 2018;73(3):696-704. doi:10.1111/all.13320
43. Katibi OS, Cork MJ, Flohr C, Danby SG. Moisturizer therapy in prevention of atopic dermatitis and food allergy: To use or disuse?. *Ann Allergy Asthma Immunol*. 2022;S1081-1206(22)00124-7. doi:10.1016/j.anai.2022.02.012
44. Cacciapuoti S, Luciano MA, Megna M, et al. The Role of Thermal Water in Chronic Skin Diseases Management: A Review of the Literature. *J Clin Med*. 2020;9(9):3047. Published 2020 Sep 22. doi:10.3390/jcm9093047
45. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a

1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287-2303. doi:10.1016/S0140-6736(17)31191-1

46. de Bruin-Weller M, Thaçi D, Smith CH, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). *Br J Dermatol*. 2018;178(5):1083-1101. doi:10.1111/bjd.16156

47. Agache I, Akdis CA, Akdis M, et al. EAACI Biologicals Guidelines-dupilumab for children and adults with moderate-to-severe atopic dermatitis. *Allergy*. 2021;76(4):988-1009. doi:10.1111/all.14690

48. Wojcikowski K, Johnson DW, Gobé G. Medicinal herbal extracts – renal friend or foe? Part one: the toxicities of medicinal herbs. *Nephrology (Carlton)*. 2004;9(5):313-318. doi:10.1111/j.1440-1797.2004.00310.x

49. Kojima R, Fujiwara T, Matsuda A, et al. Factors associated with steroid phobia in caregivers of children with atopic dermatitis. *Pediatr Dermatol*. 2013;30(1):29-35. doi:10.1111/j.1525-1470.2012.01808.x

Figure Legends:

Figure 1: Flow chart of searching and selecting guidelines

Table Legends:

Tab.1 Basic information of included guidelines

Guide ID	First Version	Location	Organization	Title	Type	Application
Werfel et al., 2016	2008	Germany	DDG	S2k guideline on diagnosis and treatment of atopic dermatitis –short version	CPG	Adults and children
Galli et al., 2016	-	Italy	SIAIP and SIDerP	Consensus Conference on Clinical Management of pediatric Atopic Dermatitis	Consensus-based guidelines	Children
Wong et al., 2017	-	Canada	ESC	Guidelines for the management of atopic dermatitis (eczema) for pharmacists	CPG	Adults and children

Guide ID	First Version	Location	Organization	Title	Type	Application
Boguniewicz et al., 2017	-	US	AAAAI	Expert Perspectives on Management of Moderate-to-Severe Atopic Dermatitis: A Multidisciplinary Consensus Addressing Current and Emerging Therapies	Consensus-based guidelines	Adults and children
Wollenberg et al., 2018	2012	Europe	EADV	Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I and part II	CPG	Adults and children
Katoh et al., 2019	2015	Japan	JDA	Clinical practice guidelines for the management of atopic dermatitis 2018	CPG	Adults and children
Chow et al., 2018	-	Asia Pacific	AADV	A clinician's reference guide for the management of atopic dermatitis in Asians	CPG	Adults and children

Guide ID	First Version	Location	Organization	Title	Type	Application
Kent. & Clark., 2018	-	India	NAPNP	Skin Deep: Simplifying Practice Guidelines for Children With Atopic Dermatitis	CPG	Children
MaHTAS, 2018	-	Malaysia	MaHTAS	Management of Atopic Eczema	CPG	Adults and children
Aoki et al., 2019	-	Brazil	BSD	Consensus on the therapeutic management of atopic dermatitis	Consensus-based guidelines	Adults and children
Damiani et al., 2019	-	Italy	SIDEMAST, ADOI, and SIDAPA	Italian guidelines for therapy of atopic dermatitis—Adapted from consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis)	CPG	Adults and children
Chiricozzi et al., 2019	-	Italy	-	Current therapeutic paradigm in pediatric atopic dermatitis: Practical guidance from a national expert panel	Consensus-based guidelines	Children

Guide ID	First Version	Location	Organization	Title	Type	Application
Rajagopalan et al., 2019	-	India	SASI	Guidelines on Management of Atopic Dermatitis in India: An Evidence-Based Review and an Expert Consensus	CPG	Adults and children
Katoh et al., 2020	2018	Japan	JSA	Japanese guidelines for atopic dermatitis 2020	CPG	Adults and children
Chan et al., 2021	2015	Taiwan, China	TDA	Taiwanese Dermatological Association consensus for the management of atopic dermatitis: A 2020 update	Consensus-based guidelines	Adults and children
Atopic Dermatitis Working Group., 2020	2008	China	Atopic Dermatitis Working Group	Chinese guideline for diagnosis and treatment of atopic dermatitis (2020)	CPG	Adults and children
Lee et al., 2021	2015	Korea	KADA	Consensus Update for Systemic Treatment of Atopic Dermatitis	Consensus-based guidelines	Adults and children
WFCMS., 2020	-	China	WFCMS	International Clinical Practice Guidelines in Traditional Chinese Medicine: Atopic Dermatitis	CPG	Adults and children

Guide ID	First Version	Location	Organization	Title	Type	Application
Kulthanan et al., 2021	-	Thailand	Dermatological Society of Thailand, etc	Clinical practice guidelines for the diagnosis and management of atopic dermatitis	CPG	Adults and children

Tab.2 Quality evaluation results of included guidelines

Guide ID	Score in each domain(%) ⁺	Score in each domain(%) ⁺	Score in each domain(%) ⁺
	1	2	3
Werfel et al., 2016	75.00	55.55	47.62
Galli et al., 2016	91.66	58.33	28.57
Wong et al., 2017	94.44	80.55	23.81
Boguniewicz et al., 2017	80.55	91.66	59.52
Wollenberg et al., 2018	88.88	91.66	91.66
Kato et al., 2019	91.66	91.66	80.95
Chow et al., 2018	58.33	38.88	71.42
Kent. & Clark., 2018	83.33	50.00	17.85
MaHTAS, 2018	100	91.66	80.95
Aoki et al., 2019	41.66	27.77	20.23
Damiani et al., 2019	36.11	25.00	23.81
Chiricozzi et al., 2019	47.22	8.33	27.38
Rajagopalan et al., 2019	66.66	55.55	55.95
Kato et al., 2020	58.33	52.77	57.14
Chan et al., 2021	50.00	27.77	21.42
Atopic Dermatitis Working Group., 2020	36.11	19.44	5.95
Lee et al., 2021	58.33	11.11	50
WFCMS., 2020	5.55	5.55	3.57
Kulthanan et al., 2021	66.66	38.88	36.9
Average	64.76	48.53	42.35

+: 1=Scope and Purpose, 2=Stakeholder Involvement, 3=Rigor of Development, 4= Clarity of Presentation, 5= Applicability, 6=Editorial Independence.

*: indicates that the difference is statistically significant

Tab.3 Keywords of included guidelines

Keywords	Guide NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Disease-related concepts	Aim Definition Clinical manifestations Pathogen														

Keywords	Guide NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Skin care	Pathogenesis														
	Complication														
	Diagnosis														
	Severity assessment														
	Avoid triggers														
	Moisturizing														
	Cleaning														
Topical therapy	Bleaching bath														
	Wet-wrap therapy														
	Topical Glucocorticoids														
	Topical calcineurin inhibitors														
Systemic treatment	Topical Antibiotics														
	Topical phosphodiesterase inhibitor														
	Glucocorticoids														
	Immunity inhibitor														
	Antibiotics														
	Antihistamine														
	Biological agents														
Alternative Medicine	Phototherapy														
Adjuvant therapy	Alternative Medicine														
	Diet														
	Essential fatty acid														
	Probiotics														
	Vitamin D														
Patient education	Allergen specific immunotherapy														
Pregnance /Lactation	Patient education														
Fingertip unit	Pregnance /Lactation														
	Fingertip unit														

Tab.4 Management advices of AD of included guidelines

Domains	Management advices
Severity assessment	Commonly used assessment scales are Scoring of Atopic Dermatitis' (SCORAD), Eczema Area and Severity Score (EASI), Patient-Oriented Eczema Measures for Eczema (POEM). Professionals can use the tool Investigators' Global Assessment (IGA).

Domains	Management advices
Moisturizing	Emollient is the most basic and important treatment strategy. There is already lots of evidences that emollient and cleansing can reduce the severity of disease and decrease medication use. There is no standard for emollients use frequency. Most guidelines recommend using adequate emollients at least twice a day, in conjunction with medication during an attack. The choice of emollient can be based on patient preference and physician recommendations. There is also no standard dosage for emollients, and fingertip units are recommended, with a dosage range of 100~200 g/week for children and 250~500 g/week for adults from Europe guide.
Cleansing	It is recommended to bathe daily and use emollients immediately after bathing. The recommended water temperature range is 27~40 and the duration is 5~10min. Choose a neutral or low pH, preservative-free cleanser, check for allergenic substances or fragrance, and choose according to season, patient's age, the site of application. Meanwhile choose with reference to the patient's preference.
Bleaching bath	Guidelines have different opinions. Some guidelines suggesting that a 0.005% bleaching bath with the addition of sodium hypochlorite may reduce the use of topical anti-inflammatory medications and antibiotics, inhibit bacterial activity. However, some guidelines have reservations about whether bleaching baths can change the severity of the disease.
Wet-warp therapy	Wet-warp therapy (WWT) consists of a double layer of gauze or tubular bandage, with a wet inner layer and a dry outer layer. Commonly used in moderate-to-severe AD, acute phase, exudate, corrosive lesions during exacerbation. WWT can be used with emollient cream alone or in combination with TCS. WWT has been shown to increase the absorb of TCS and reduce disease severity and water loss during flares. WWT is also a relatively safe and effective treatment for children, with an age recommendation of over 6 months and a duration of use usually not exceeding 14 days. Side effects of glucocorticoids after systemic absorption need to be noted.

Domains	Management advices
Topical glucocorticoids	<p>1. Principle: Adequate strength, dosage and reasonable application 2. Dosage: The average dose is 15g per month for infants, 30g per month for children, and 60~90g per month for adolescents and adults. 3. Frequency: For mild AD, 1~2 times per day during flare-ups and 2~3 times per week for maintenance treatment. 4. Selection factors: efficacy, formulation, patient age and site of application, severity, patient preference, and costs. 5. Medication strength grade: Mostly divided into 4 levels (very strong, strong, medium, weak), Japan is divided into 5 levels (strongest, very strong, strong, medium, weak) 6. Special position: The facial area, especially the eyes, neck, scalp of infants, skin folds, genitals need to be used with caution. 7. Length of use: No more than 6 months 8. Side effect: Be alert to systemic or local side effects caused by improper application, frequency of use, and improper duration of use</p>
Topical Calcineurin Inhibitors	<p>Most commonly used drugs are Tacrolimus and Pimecrolimus. Children are of special medication age. 1. Time to use: Generally, it is used in the acute period that is a TCS replacement therapy. TCI can be used for special location like face and genitals when TCS is not tolerated or side effects occur. 2. Age: 1% Pimecrolimus is for children over 2 years or older. 0.03% Pimecrolimus for patients aged 2~15 years. 0.1% tacrolimus is for adolescents over 16 years or older. 3. Frequency: 2~3times per week for active treatment. 4. Dosage: 0.03% Tacrolimus: 1g for children 2~5 years (weight < 20 kg), 2~4g for 6~12 years (weight 20~50 kg) and max 5 g for 13 years or older (weight [?] 50 kg). 5. Pay attention to sunscreen when using TCI. Routine application is not recommended for non-infectious AD. AD is often caused by Staphylococcus aureus when accompanied by skin infections, so it is recommended to consider topical antibiotic treatment in the presence of obvious signs of infection, but long-term use of topical antibiotics is not recommended and may increase the risk of drug resistance and sensitization. Commonly used drugs can be seen as fusidic acid and mupirocin, and the duration of use is recommended to last 7~10 days or no more than one week, 2~3 times per day.</p>
Topical Antibiotics	

Domains	Management advices
Phosphodiesterase Inhibitor	Commonly used drugs include Crisaborole and Apremilast which have increased evidences in recent years and have been shown to reduce severity. Phosphodiesterase inhibitor are approved in some countries for mild and moderate AD over two years of age. Consider the cost when using.
Glucocorticoids	Short-term use in moderate to severe acute attacks is recommended. Avoid side effects of long-term use. Use for a period of no more than 1~2 weeks. More caution when used by children. The Italian consensus does not recommend use in children, as rebound or worsening of symptoms may occur after discontinuation of the drug.
Immunity Inhibitor	As second-line therapeutic agents, commonly used are cyclosporin, azathioprine, mycophenolate mofetil, and methotrexate as treatment options for refractory or severe AD, which are over-indicated for both children and adolescents, with monitoring for adverse effects during use. They may be teratogenic when used in pregnant women under strict indications. The dose used varies from country to country.
Systematic Antibiotics	Systematic use of antibiotics is recommended when there are obvious signs of infection. Cephalosporin is recommended as the first choice, avoid long-term use and use for no longer than two weeks.
Antihistamine	Initially most guidelines did not recommend antihistamines because there was little evidence of their effectiveness in controlling pruritic symptoms, and because sedating antihistamines may affect sleep quality in children. As research evidence increased, some guidelines considered as adjunctive therapy, combined with topical anti-inflammatory agents to reduce pruritic symptoms, and recommended the use of non-sedating antihistamines. Patients with sleep disorders could be given sedating antihistamines for a short time.

Domains	Management advices
Biological Agents	Evidence on the efficacy and safety of biologic agents for the treatment of AD is gradually increasing, but still as a complementary treatment to AD therapy or in refractory, moderate-to-severe patients. Dupilumab is the first biologic agent for moderate-to-severe AD adults that approved by FDA and Europe standards in 2017. Dupilumab was approved by FDA for use in children over six years of age in 2020. It is recommended to use in combination with topical emollients and anti-inflammatory drugs, and to consider the cost effectiveness. Omalizumab, ustekinumab, rituximab, mepolizumab, nemolizumab and alefacept are not recommended due to limited evidence.
Phototherapy	Phototherapy is the second-line treatment for AD. Common forms of phototherapy are UVA-1 therapy for acute flares and UVB narrowband therapy for severe chronic maintenance treatment. Most guidelines recommend the use of phototherapy beyond the age of 10~18 years and 2~3 times a week. Selection of phototherapy modality based on feasibility, cost, patient skin type, skin cancer history, and use of photosensitizing drugs.
Alternative Medicine	Evidence is insufficient to recommend the use of alternative medicine such as herbal medicine, acupuncture, massage, aromatherapy, homeopathy, etc. Patients using alternative medicine should be informed of the potential hazards and should not replace conventional treatment.
Diet	Diet restriction is not recommended unless there is a clear history of allergy or a positive oral irritation test. If it is necessary, it is recommended that it be done under expert guidance to avoid dietary errors or malnutrition, and only after informing family members of the limited benefits and possible harms of elimination diets. Infants are recommended to be breastfed until four months of age, and diversity is observed when food is introduced between four and six months. Supplementation is not recommended to administer AD. Diet restriction is not recommended for pregnant and breastfeeding women to prevent AD.

Domains	Management advices
Essential fatty acid	Routine supplementation with essential fatty acids is not recommended for the management of AD because of limited evidence. However, some guidelines suggest that oral essential fatty acid and topical application as a component of emollients is recommended in some cases.
Probiotics	Although there are studies have confirmed that probiotics can reduce AD severity compared to controls, there is no evidence to support the benefits of probiotics in children. The routine use of probiotics for AD management is not recommended.
Vitamin D	Limited evidence finds that vitamins may be useful for AD management, but not enough to support that vitamin D supplementation can be a treatment method.
Allergen specific immunotherapy;	ASIT is not recommended as a routine treatment option and can be used for patients with combined allergic rhinitis, bronchial asthma, dust mite, pollen allergy, or moderate to severe exposure to allergens.
Patient education	Patient education is needed throughout the AD management process. Reducing steroid phobia can effectively increase compliance with medication and reduce relapse. Patient education needs a professional multidisciplinary team to carry out and adopt a specific educational model for different cultures.
Fingertip unit	When using emollients, TCS and TCI it is recommended to use fingertip unit to prevent over or under dosage. FTU is the dose squeezed from the tip to the first joint along the index finger in adults (~0.5 g). 1 FTU is approximately equivalent to taking an appropriate amount of thin and evenly applied to the skin area equivalent to 2 adult hands, the dose required for children is age-related.