CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Emollient Treatments for Atopic Dermatitis: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	January 14, 2019
Report Length:	21 Pages

CADTH

Authors: Ron Pohar, Suzanne McCormack

Cite As: Emollient Treatments for Atopic Dermatitis: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa: CADTH; 2019 Jan (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Abbreviations

EASI	Eczema Area and Severity Index
MCID	Minimally clinically important difference
RCT	Randomized controlled trial
TEWL	Transepidermal water loss

Context and Policy Issues

Atopic dermatitis is a skin disease that is chronic and inflammatory in nature; essential features include pruritus and eczematous lesions.[1] Pruritus is the key feature of atopic dermatitis that contributes to the significant burden of this condition, including its significant impact on quality of life.[2] Other commonly encountered clinical features of atopic dermatitis include skin dryness, erythema, oozing and crusting of the lesions.[2] Atopic dermatitis can follow a disease course that is continuous for an extended period of time or it can follow a relapsing-remitting disease course, characterized by flare-ups.[1] The key goals of treatment of atopic dermatitis are to reduce symptoms, prevent exacerbations, and reduce the risk of complications, such as secondary infections.[1,2] Recent, reliable estimates of the prevalence of atopic dermatitis in the pediatric and adult population in Canada are not available, but US prevalence rates are estimated to be 11% in children and 7% in adults.[3]

Management of atopic dermatitis requires a multistep approach, with emollients being one of the key treatment modalities.[1 2] Emollients are used to help repair and maintain the skin's epidermis, through frequent and generous application.[1] Emollients form an occlusive layer on the skin, which helps to soften it and reduce water loss. Emollients are one of the key ingredients found traditional moisturizers, along with humectants, such as glycerin, urea and lactic acid, which help to bind water in the skin's stratum corneum, and occlusive agents that create a barrier on the skin to prevent transepidermal water loss (TEWL). Individuals with atopic dermatitis may experience irritation or allergic reactions to products that contain fragrances, perfumes, and other irritants.[1] Thus, such products are typically not recommended.[1]

The Eczema Society of Canada has a Seal of Acceptance program *"where products are reviewed to earn recognition from the Eczema Society as an accepted choice for people with sensitive skin."*[4] This report aimed to summarize the evidence regarding the clinical effectiveness, cost-effectiveness and guidelines of emollient treatments with "Seal of Acceptance" from the Eczema Society of Canada for atopic dermatitis. However, no evidence of cost-effectiveness was identified specific to these products, so only evidence of clinical effectiveness and guidelines are reported.

Research Questions

1. What is the clinical effectiveness of emollient treatments for the management of atopic dermatitis?
2. What is the cost-effectiveness of emollient treatments for management of atopic dermatitis?
3. What are the evidence-based clinical practice guidelines for the use of emollient treatments in the management of atopic dermatitis?

Key Findings

Two systematic reviews concluded that emollients were beneficial in the treatment of atopic dermatitis, but that there was insufficient evidence to recommend one over another or that they could be used as a stand-alone treatment. There were no conclusions made specific to products that had the Seal of Acceptance from the Eczema Society of Canada.

Two evidence-based clinical guidelines emphasized the importance of emollients for the management of atopic dermatitis; however, no recommendations were specific to products with the Seal of Acceptance from the Eczema Society of Canada and it was stated that there was insufficient evidence to recommend one product over another.

No evidence of the cost-effectiveness of emollient treatments with the Seal of Acceptance from the Eczema Society of Canada was identified.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, economic studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and November 30, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients of any age with atopic dermatitis (eczema)
Intervention	Emollient treatments (with the “Seal of Acceptance” from the Eczema Society of Canada), alone or in combination
Comparator	No treatment
Outcomes	Q1: Clinical effectiveness (e.g., change in atopic dermatitis severity, health-related quality of life; change in use of topical active treatment; prevention of flares or infection; visits to a primary care provider; adverse events such as itching, stinging or sensitization) Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Guidelines with unclear methodology and those that did not address emollients with the Seal of Acceptance from the Eczema Society of Canada were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using AMSTAR II checklist,[5] and guidelines were assessed with the AGREE II instrument.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 131 citations were identified in the literature search. Following screening of titles and abstracts, 96 citations were excluded and 35 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full text review. Of these potentially relevant articles, 32 publications were excluded for various reasons, and 4 publications met the inclusion criteria and were included in this report. These comprised two systematic reviews and two evidence-based guidelines. No relevant economic evaluations were identified. Appendix 1 presents the PRISMA[7] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2, Table 2 and Table 3. No relevant economic evaluations of Seal of Acceptance emollients were identified.

Study Design

There were two relevant systematic reviews included in this Rapid Response, one published in 2017 [8] and the other published in 2015 [9] (Appendix 2, Table 2). Both had search periods up to 2015, with the 2017 publication having a cut-off of December of 2015 and the 2015 publication having a cut-off of January of 2015. There was no overlap in the included studies in the two systematic reviews relevant to this Rapid Response. Only RCTs were included in van Zuuren 2017 with no restriction on blinding; however, Lindh 2015 included only interventional clinical studies but did not require randomization or a control group for some outcomes (Appendix 2, Table 2). Specifically, for transepidermal water loss (TEWL), which measures water evaporation through the skin and skin barrier function, single group, before and after studies were eligible for inclusion. For both systematic reviews, any emollient or moisturizer was the intervention of interest; however, only studies with data relevant to emollient treatments with the Seal of Acceptance were considered for this Rapid Response. For van Zuuren 2017, there were 77 studies included in the systematic review, but the intervention of interest was emollient treatments with the Seal of Acceptance in two studies (one study of Cetaphil Restoraderm and one study of Eucerin Eczema Relief). Similarly, Lindh 2015 also included studies that evaluated other emollient

treatments, not only those with the Seal of Acceptance. Lindh 2015 also included studies of patients with other types of dermatitis similar to atopic dermatitis. Of the 48 studies included in the Lindh 2015 systematic review, two studies (both of which were contained in a single publication) met the selection criteria for this Rapid Response and assessed Eucerin Eczema Relief. The patients in the two studies that were relevant to this Rapid Response had atopic dermatitis, despite the systematic review itself including studies of patients with other similar skin disorders.

Two relevant guidelines were identified, one developed by the Malaysian Ministry of Health in 2018[10] and one developed by the American Academy of Dermatology in 2014 (Appendix 2, Table 3).[11] Both guidelines used systematic literature searches to identify the literature. The guideline from the Malaysian Ministry of Health[10] rated the quality of the evidence using the categorization developed by the US/Canadian Preventative Services Task Force and reported using GRADE to assign strengths of recommendations but the strengths of recommendations were not reported in the current document which was available in draft format. For the American Academy of Dermatology guideline,[11] evidence was rated according to the Strength of Recommendation Taxonomy (SORT), and the strength of recommendation was rated as A, B or C as outlined in Table 3. For both guidelines, consensus was used to formulate the recommendations.

Country of Origin

One systematic review was from The Netherlands[8] and one was from Sweden[9]. For the guidelines, one was from Malaysia[10] and one was US-based.[11]

Patient Population

The van Zuuren 2017 systematic review included studies of patients with eczema, atopic dermatitis, or atopic eczema diagnosed by a physician using recognized diagnostic criteria.[8] There was no restriction placed on setting (i.e., inpatient, outpatient, community). Of the two studies that were relevant to this Rapid Response, one study included 127 patients with mild to moderate eczema[12] and one study included 45 patients with eczema.[13] The Lindh 2015 systematic review[9] included two studies of patients with atopic dermatitis; however, it was not specified if standard diagnostic criteria were required.[13] Each study included 66 participants in total.

For both of the included guidelines,[10,11] the target population was patients with atopic dermatitis (adults and children), with the intended users of the guidelines being those that provide primary care to this group of patients. The Malaysian Ministry of Health guideline[10] clearly stated that it was intended for use by anyone who provided care for this group, whereas the American Academy of Dermatology guideline[11] was not as explicit as to whom the guideline's intended users were.

Interventions and Comparators

In the van Zuuren 2017 systematic review,[8] one study compared Cetaphil Restoraderm on one leg twice daily with no moisturizer on the other leg twice daily for 27 days.[12] The other study compared Eucerin Eczema Relief once daily in one group of patients to a group of patients that received no moisturizer over six months.[13]

In the Lindh 2015 systematic review,[9] there was one report included[14] that presented results of two studies of Eucerin Eczema Relief applied twice daily compared with no treatment over a two week treatment period.

For the guidelines that were included, evidence related to specific emollients treatment use in the management of atopic dermatitis was presented.[10,11]

Outcomes

Outcomes reported in the van Zuuren 2017 systematic review[8] included a 0 to 4 dryness scale (no details reported on scale anchors), TEWL, and flares (including proportion of patients with flares, median time to flare and the hazard ratio for flares). The TEWL is a measure of water evaporation through the skin and skin barrier function. A higher value for TEWL suggests skin barrier impairments, and lowers TEWL suggests healthy skin. Thus, a decrease in TEWL would suggest an improvement.[15] There were no minimally important differences (MCIDs) found for the dryness scale or the TEWL. In the two studies of Eucerin Eczema Relief in the Lindh 2015 systematic review,[9] the outcome reported was TEWL.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 4 and Table 5.

The van Zuuren 2017 systematic review[8] satisfied the majority of the criteria of the AMSTAR II critical appraisal tool for systematic reviews (Appendix 3, Table 4). Specifically, the literature search strategy appeared to be comprehensive, searching multiple databases. Literature screening, study selection and data extraction were performed in duplicate and detailed data tables were included as supplemental information. The quality of the included studies was assessed with the Cochrane Risk of Bias Tool, and the results of this quality assessment was considered in making conclusions based upon the individual studies. The results of the studies relevant to this Rapid Response were summarized narratively. Limitations included a lack of explicit research questions and no clearly stated rationale for including study designs other than RCTs.

The Lindh 2015 systematic review[9] satisfied some key criteria of the AMSTAR II critical appraisal tool for systematic reviews such as having a comprehensive search strategy with duplicate data extraction. Again, the Cochrane Risk of Bias Tool was used for quality assessment and was used in making conclusions. Limitations included a single reviewer for data extraction without data verification, lack of a statement that an a priori protocol was followed, lack of clear research questions, and no rationale for allowing different study designs for different outcomes.

The guideline from the Malaysian Ministry of Health[10] met all of the criteria of the AGREE II checklist with the scope and purpose being clearly defined and stakeholder involvement being sought (Appendix 3, Table 5). Methods for development were rigorous, with systematic literature searches, duplicated literature selection, the strengths and limitations of the evidence being considered and recommendations being explicitly linked to the evidence and clearly articulated. Further, there was a plan developed for implementation and the guideline was independent of conflict of interest in its development.

The American Academy of Dermatology Guideline[11] met the majority of the criteria of the AGREE II checklist but had some limitations. In particular, stakeholder involvement in the guideline formulation process beyond the American Academy of Dermatology itself was lacking. Further, there was no consideration of barriers to implementation or application, no advice or tools for practice, no consideration given to resource implications of applying the guideline and no monitoring and auditing criteria provided.

Summary of Findings

Clinical Effectiveness of Emollient treatments (with the "Seal of Acceptance" from the Eczema Society of Canada)

The main study findings and authors' conclusions are found in Appendix 4, Table 6 and Table 7.

In the van Zuuren 2017 systematic review[8] Cetaphil Restoraderm was assessed in one study (Appendix 4, Table 6). One study found that the mean (SD) change in dryness with Cetaphil Restoraderm was -1.15 (0.41) and -0.91 (0.58) with no moisturizer.[12] For TEWL, the mean (SD) change was -1.59 (NR) with Cetaphil Restoraderm and -0.42 (1.13) with no moisturizer.[12] No statistical analysis was reported but differences were stated as statistically significant. No adverse events were reported in either group. In the study that assessed Eucerin Eczema Relief, the proportion of patients with flares was lower with Eucerin compared with no moisturizer and the median time to flare was longer (more than 180 days versus 28 days). The hazard for flares was increased with no moisturizer (4.47; 95% CI: 1.57 to 14.34).[13] The authors of the systematic review concluded that moisturizers were effective in prolonging the time to flare and decreasing the rate of flare. The authors suggested that there was insufficient evidence to recommend one moisturizer over another or that moisturizers could be used as a stand-alone treatment. There were no conclusions made specific to the Seal of Acceptance moisturizers.

In the two studies of Eucerin Eczema Relief with results reported in the Lindh 2015 systematic review,[9] the TEWL decreased from baseline. The difference in change from baseline in TEWL was -22.4% in Study I ($P < 0.05$) and -21.2% in Study II ($P = 0.035$).[14] The authors of the systematic review concluded that moisturizers were beneficial in atopic dermatitis. It should be noted that this was a general conclusion for all of the moisturizers included in the review and not specific to those with the Seal of Acceptance from the Eczema Society of Canada.

Cost-Effectiveness of Emollient treatments (with the "Seal of Acceptance" from the Eczema Society of Canada)

No evidence of cost-effectiveness was identified for emollient treatments with the "Seal of Acceptance" from the Eczema Society of Canada.

Guidelines related to use of Emollient treatments (with the "Seal of Acceptance" from the Eczema Society of Canada)

Both the Malaysian Ministry of Health [10] and the American Academy of Dermatology [11] guideline indicate that there is insufficient evidence to recommend one emollient over another (Appendix 4, Table 7). No other guideline recommendations for the use of emollients in atopic dermatitis were specific to those with the Seal of Acceptance from the Eczema Society of Canada. Other guidelines related to the use of emollients in general in atopic dermatitis can be found in Appendix 5.

Limitations

There were two systematic reviews included in this Rapid Response, neither of which restricted the intervention to trials of emollient treatments with the Seal of Acceptance from the Eczema Society of Canada. As such, the conclusions made were not specific to the selection criteria for this Rapid Response. Further, any pooled estimates of treatment effect

reported in the systematic reviews could not be included in this Rapid Response as they were not relevant to the interventions of interest. While the two systematic reviews included a large number of studies, only four studies in total evaluated emollient treatments that had the Seal of Acceptance. In those four studies, only two different emollients were assessed. Thus, the majority of the emollients with the Seal of Acceptance were not evaluated in the two systematic reviews captured in the literature search. Further, the two systematic reviews had search cut-offs in 2015. It is not clear if more recent trials are available as the literature search strategy for this Rapid Response focused on health technology assessments, systematic reviews, and meta-analyses to address the question of clinical effectiveness. There was limited evidence available on adverse effects, which were reported in only one included study. The findings of the individual studies were difficult to interpret for several reasons. There was no information presented in the systematic reviews about study power, no presentation of the actual results of the statistical testing (for the van Zuuren review) and no details of the statistical methods used to analyze the outcomes. Without this information, it was not possible to assess the validity of the authors' conclusions. Further, for TEWL and the five-point dryness scale, there were no MCIDs to compare the amount of improvement to. Thus, it was not possible to interpret whether the amount of improvement would impact patients in a meaningful way. Finally, majority of the included studies within the two systematic reviews were rated as having a high risk of bias by the systematic review authors.

There was no evidence of the cost-effectiveness of emollients with the Seal of Acceptance from the Eczema Society of Canada. Further, there were no guideline recommendations specific to these emollients, only statements that there was insufficient evidence to support the recommending specific emollients based on available evidence. One of the two guidelines was from the Malaysian Ministry of Health. While the context of this guideline may be different from that of Canada in terms of applicability and implementation, the evidence base is likely still generalizable. As such, the statement that there is insufficient evidence that one emollient is more effective than another remains relevant to the Canadian context. Further, this statement is in agreement with the guideline from the American Academy of Dermatology.

Conclusions and Implications for Decision or Policy Making

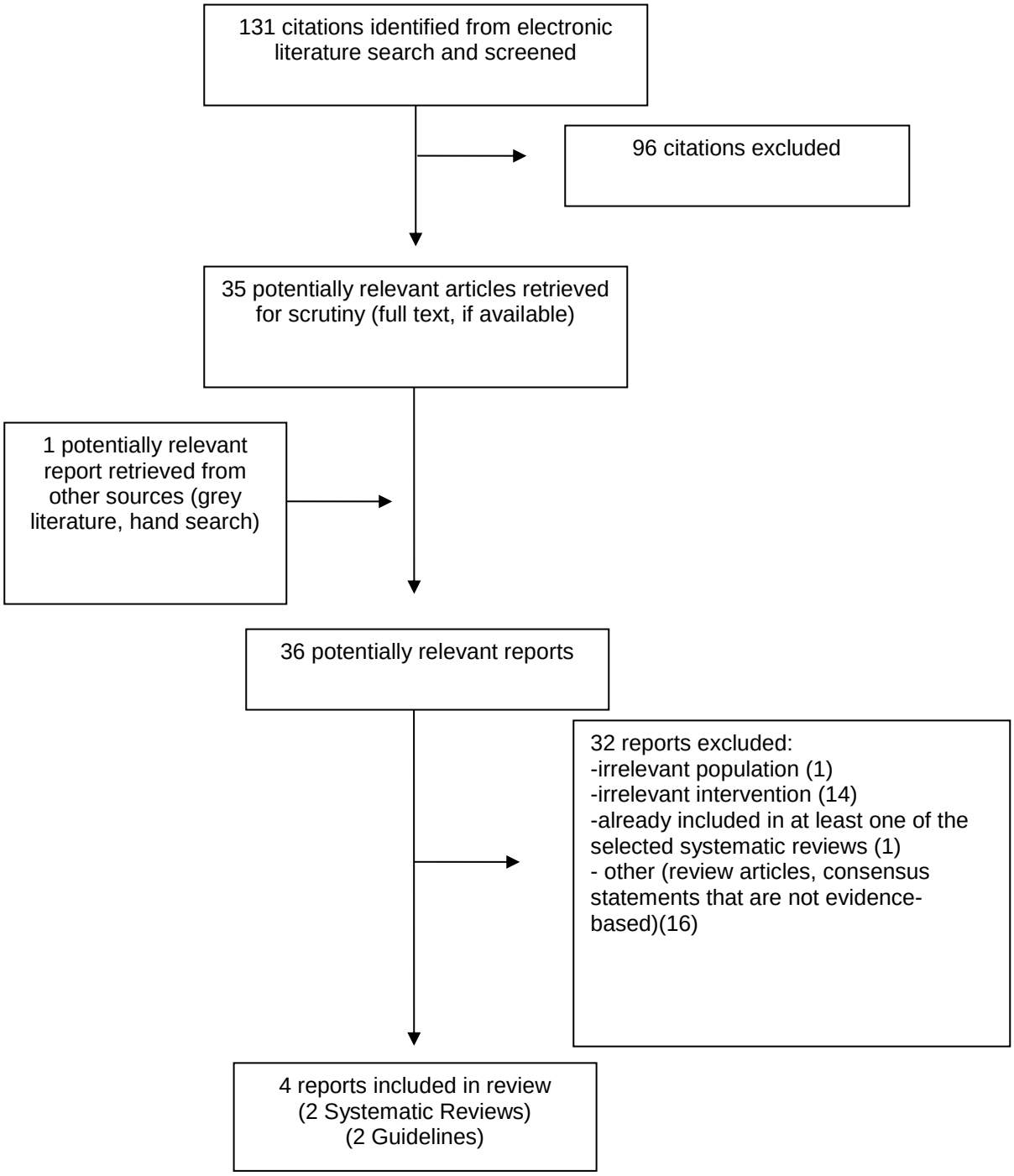
Two systematic reviews and two guidelines were included in this Rapid Response. The two included systematic reviews provided evidence of efficacy of Cetaphil Restoraderm and Eucerin Eczema Relief. Compared with no moisturizer, Cetaphil Restoraderm was associated with a greater reduction in dryness and less water loss from the skin, but the clinical importance of these changes was unclear. Similarly, Eucerin Eczema Relief also reduced water loss from the skin compared with no moisturizer, but again the clinical benefit was not clear for this outcome. As well, Eucerin Eczema Relief prolonged the time to flare and had a lower flare rate than with no moisturizer. It was generally concluded based on systematic reviews that emollient treatments had a beneficial effect in atopic dermatitis; however, these conclusions were not specific to emollient treatments with the Seal of Acceptance from the Eczema Society of Canada as the reviews evaluated many different products. Only two products with the Seal of Acceptance were assessed in the included studies. Further research assessing the efficacy of other emollient treatments with the Seal of Acceptance may provide evidence to support the use of additional products other than Eucerin Eczema Relief and Cetaphil Restoraderm. The two included guidelines state that there is insufficient evidence to recommend specific emollient treatments. Given the current guideline recommendations, it is unclear if there is a clear rationale for

preferentially recommending products with the Seal of Acceptance from the Eczema Society of Canada.

References

1. Weidinger S, Novak N. Atopic dermatitis. *Lancet.* 2016;387(10023):1109-1122.
2. Weston W. Treatment of atopic dermatitis (eczema). In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2018: www.uptodate.com. Accessed 2018 Nov 30.
3. Atopic dermatitis quality of life report: moderate-to-severe disease 2016/2017 survey results. Keswick (ON): Eczema Society of Canada; 2017: https://eczemahelp.ca/wp-content/uploads/2017/08/ESC_QUALITY_OF_LIFE_REPORT_2017.pdf. Accessed 2019 Jan 4.
4. Eczema Society of Canada seal of acceptance statement. 2019; https://eczemahelp.ca/legal-and-privacy/#section=seal. Accessed 2019 Jan 4.
5. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2019 Jan 4.
6. Agree Next Steps Consortium. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 Jan 4.
7. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
8. van Zuuren EJ, Fedorowicz Z, Arents BWM. Emollients and moisturizers for eczema: abridged Cochrane systematic review including GRADE assessments. *Br J Dermatol.* 2017;177(5):1256-1271.
9. Lindh JD, Bradley M. Clinical Effectiveness of Moisturizers in Atopic Dermatitis and Related Disorders: A Systematic Review. *Am J Clin Dermatol.* 2015;16(5):341-359.
10. Ministry of Health Malaysia, Dermatological Society of Malaysia, Academy of Medicine Malaysia. Management of atopic eczema (DRAFT). Putrajaya (MY): Malaysian Health Technology Assessment Section (MaHTAS); 2018: http://www.moh.gov.my/index.php/file_manager/dl_item/545746706269424359573575 5a5849764d6a41784f43394e5a576b7652484a685a6e526651314248583031686 26d466e5a57316c626e526662325a665158527663476c6a5830566a656d5674595335775a47593d. Accessed 2019 Jan 4.
11. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014;71(1):116-132.
12. Simpson E, Bohling A, Bielfeldt S, Bosc C, Kerrouche N. Improvement of skin barrier function in atopic dermatitis patients with a new moisturizer containing a ceramide precursor. *J Dermatolog Treat.* 2013;24(2):122-125.
13. Weber TM, Samarin F, Babcock MJ, Filbry A, Rippke F. Steroid-Free Over-the-Counter Eczema Skin Care Formulations Reduce Risk of Flare, Prolong Time to Flare, and Reduce Eczema Symptoms in Pediatric Subjects With Atopic Dermatitis. *J Drugs Dermatol.* 2015;14(5):478-485.
14. Weber TM, Babcock MJ, Herndon JH, Jr., et al. Steroid-free emollient formulations reduce symptoms of eczema and improve quality of life. *J Drugs Dermatol.* 2014;13(5):589-595.
15. Akdeniz M, Gabriel S, Lichterfeld-Kottner A, Blume-Peytavi U, Kottner J. Transepidermal water loss in healthy adults: a systematic review and meta-analysis update. *Br J Dermatol.* 2018;179(5):1049-1055.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
van Zuuren, 2017, The Netherlands[8]	Randomized controlled trials. 77 studies were included in total. 2 studies evaluated products with the Eczema Society of Canada Seal of Acceptance.	People with eczema, atopic dermatitis, or atopic eczema diagnosed by a physician using recognized criteria for diagnosis.	Intervention – any moisturizer alone or in combination with topical anti-inflammatory treatment. Comparator – no moisturizer, placebo vehicle, or anti-inflammatory treatment.	Participant assessed disease severity; satisfaction with moisturizer; adverse events; investigator assessed disease severity; flares; use of topical anti-inflammatory treatment; skin barrier function; health-related quality of life. Length of follow-up ranged from 2 weeks to 6 months.
Lindh, 2015 Sweden[9]	Eligible designs depended on the outcome. Stratum corneum hydration and TEWL – before/after clinical studies were eligible for inclusion. Clinical outcomes required a control (parallel group, cross-over, or within-subject comparison between different skin areas). 48 studies were included in total. 2 studies evaluated products with the Eczema Society of Canada Seal of Acceptance.	People with atopic dermatitis, irritant hand dermatitis, or ichthyosis vulgaris.	Intervention – one or more emollient. Comparator – no emollient, another emollient, or the vehicle of the investigated moisturizer. Combinations of emollients and corticosteroids were included if the corticosteroid exposure was the same between groups.	Clinical effectiveness (e.g., treatment success, relapse, SCORAD or similar scoring system) Trans-epidermal water loss (TEWL) Stratum corneum hydration Length of follow-up ranged from 90 minutes to 6 months.

SCORAD = Severity Scoring of Atopic Dermatitis ; TEWL= Transepidermal water loss

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Malaysian Ministry of Health, 2018[10]						
Those involved in the management of atopic eczema at any healthcare level.	Treatment of atopic dermatitis in primary care.	For emollients: symptoms, flare, corticosteroid use, severity, hydration.	Evidence collection: Systematic database searches, review of other guidelines. Evidence selection: Literature was selected by two reviewers. Synthesis: All literature was summarized in evidence tables which were used for discussion at development committee meetings.	Level of evidence was evaluated according to the US/Canadian Preventative Services Task Force: "I - Evidence from at least one properly randomised controlled trial II -1 Evidence obtained from well-designed controlled trials without randomisation II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group II-3 Evidence from multiple time series with or without intervention. III Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees" p.6	The development group members met 19 times to discuss the literature and formulate recommendations, which had to be agreed upon by the development group and review committee. Where there was insufficient evidence, consensus was used to make a recommendation; however, it is stated that the guideline was "*based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.*" Grading of recommendations followed the principles of GRADE but strengths of recommendations were not presented in the document.	Guideline was posted for feedback from interested parties and reviewed externally.
American Academy of Dermatology, 2014[11]						
Not clearly stated, but appears to be	Management and treatment of atopic dermatitis	Hydration of the skin, symptoms and signs of AD,	Evidence collection: Systematic	Evaluated using Strength of Recommendation	The process used for reaching consensus was not described, but it was	The guideline was open for review and

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
developed for primary care providers of individuals with atopic dermatitis.	with topical therapies	use of prescription anti-inflammatories, flares.	database searches, handsearching of reference lists, review of previous guidelines. Evidence selection: based on relevancy and the highest level of available evidence for each clinical question was selected. Synthesis: Evidence tables were generated and used to develop recommendations	Taxonomy (SORT): "I.Good-quality patient-oriented evidence (i.e. evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life). II.Limited-quality patient-oriented evidence. III.Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence (i.e. evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes)."p3	stated that " *Clinical recommendations were developed based on the best available evidence tabled in the guideline".* Recommendations were ranked according to the following levels: "A. Recommendation based on consistent and good-quality patient-oriented evidence. B. Recommendation based on inconsistent or limited-quality patient-oriented evidence. C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence."p.3	comment by the membership of the American Academy of Dermatology. It was approved by the Board of Directors

AD = Atopic dermatitis; GRADE=Grading Recommendations, Assessment, Development and Evaluation; SORT = Strength of Recommendation Taxonomy

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[5]

Strengths	Limitations
van Zuuren, 2017, The Netherlands[8]	
The authors stated that the review as conducted according to an a priori protocol. The literature search strategy appeared to be comprehensive (searching multiple databases), but was only up to date as of December 2015. Study selection and data extraction were performed in duplicate. Supplemental information with details of the included studies is available. The Cochrane Risk of Bias Tool was used to assess study quality and was considered in interpreting the results. The authors had no funding sources or conflict of interest. The results were described narratively for the emollients of interest to this Rapid Response; thus, items related to meta-analysis were not considered.	The PICOs of the review were clearly stated; however, there was no research question included in the report. Only RCTs were included in the systematic review. There was no rationale provided for this decision. References to the excluded studies are provided, but there is no rationale for exclusion. The funding source of the included studies was not reported in the review.
Lindh, 2015 Sweden[9]	
The literature search appeared to be comprehensive, with multiple databases searched; however the last search was as of January 16, 2015. Study selection was performed in duplicate. The Cochrane Risk of Bias Tool was used to assess study quality and was considered in interpreting the results. The authors had no funding sources or conflict of interest. The study results were summarized narratively due to heterogeneity in design and duration of follow-up.	There was no clear research question for the systematic review, but the PICOs for the review were clearly stated. Different study designs were permitted for different outcomes. There was no rationale provided for this. It was unclear if the review followed an a priori protocol. Data extraction was performed by one person. There was no list of excluded studies or reasons for exclusion. The funding source of the included studies was not reported in the review.

PICO = Population, intervention, comparator, outcome; RCT = Randomized controlled trial

Table 5: Strengths and Limitations of Guidelines using AGREE II[6]

Item	Guideline	
	Malaysian Ministry of Health, 2018[10]	American Academy of Dermatology, 2014[11]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes (presented in a table within the document).
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes (All patients with atopic eczema).	Unclear (stated as "management and treatment of atopic dermatitis with topical therapies" but specific population not described).
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes (Dermatology, family medicine, pediatrics, pharmacy, dieticians).	No (only dermatology is represented).
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes (posted for feedback by interested groups)	No (only reviewed by dermatologists).
6. The target users of the guideline are clearly defined.	Yes (those involved in the management of atopic eczema at any healthcare level).	No (not explicitly stated).
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	Yes (standard systematic review methods described).	Yes (methods for review are described).
8. The criteria for selecting the evidence are clearly described.	Yes (selected by two reviewers).	Yes (methods for selection are generally described).
9. The strengths and limitations of the body of evidence are clearly described.	Yes (guidelines indicate where evidence is lacking).	Yes.
10. The methods for formulating the recommendations are clearly described.	Yes (process used for meeting, consensus described).	Yes (process used for meeting, consensus described).
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes – Adverse effects of emollients considered.	Yes – Adverse effects of emollients and other topicals is considered.
12. There is an explicit link between the recommendations and the supporting evidence.	Yes – For most recommendations, the literature is cited.	Unclear – While the literature is discussed, it is separate from the recommendations. The level of evidence for the recommendations is not presented.
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Yes – However, only dermatologists.

Table 5: Strengths and Limitations of Guidelines using AGREE II[6]

Item	Guideline	
14. A procedure for updating the guideline is provided.	Yes – Guideline to be updated every four years.	Yes – Guideline to be updated every five years.
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	Yes – brief section on implementation included that identifies barriers.	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes – briefly addressed.	No
20. The potential resource implications of applying the recommendations have been considered.	Yes – briefly addressed in section on implementation.	No
21. The guideline presents monitoring and/or auditing criteria.	Yes – briefly addressed in section on implementation.	No
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Yes – Appears to be independent.	Yes – Members with competing interests recused themselves when needed.
23. Competing interests of guideline development group members have been recorded and addressed.	Yes – No competing interests.	Yes – Competing interests noted.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
van Zuuren 2017[8]	
Cetaphil Restoraderm on one leg versus no moisturizer on other[12] *Mean change (SD) in 5-point dryness scale (0-4):* Cetaphil Restoraderm: -1.15 (0.41) No moisturizer: -0.91 (0.58) *Mean (SD) change in TEWL* Cetaphil Restoraderm: -1.59 (NR) No moisturizer: -0.42 (1.13) No adverse events in either group No statistical analysis reported but the difference was reported to be statistically significant. **Eucerin Eczema Relief in one groups versus no emollient in other[13]** *Proportion with flare* Eucerin Eczema Relief: 4/20 No emollient: 15/23 *Median time to flare* Eucerin Eczema Relief: > 180 days No emollient: 28 *HR for flare:* 4.47 (95% CI: 1.57 to 14.34) in favour of Eucerin Eczema Relief No statistical analysis reported except for 95% CI for HR; no conclusions reported due to a high risk of bias related to lack of blinding.	No conclusions were made specific to the Seal of Acceptance Moisturizers. "*In conclusion, moisturizers prolong the time to flare, decrease the number of flares and reduce the amounts of topical corticosteroids needed to control eczema. Topical anti-inflammatory treatment in combination with moisturizers yields better results than without moisturizers. The review did not show convincingly that some moisturizers perform better than others, that moisturizers alone improve disease severity sufficiently or that they are suitable as sole treatment of (very) mild eczema. Furthermore, the effects of moisturizers in the different phases of the disease, such as acute, chronic or in between flares, remain unclear. In view of the impact on adherence, studies should report adverse events more thoroughly and a clear distinction must be made between adverse events and unwanted effects (e.g. cosmetic acceptability, 'feel' on the skin and staining).*" P.1264
Lindh, 2015 Sweden[9]	
Eucerin Eczema Relief versus No Emollient[14] **Study I** Mean Difference in Within Person Percent Change from Baseline in TEWL (2 weeks) **-22.4% (P <0.05)** **Study II** Mean Difference in Within Person Percent Change from Baseline in TEWL (2 weeks) **-21.2% (P = 0.035)**	No conclusions were made specific to the Seal of Acceptance Moisturizers. *"In this systematic review, we found convincing evidence that moisturizer treatment is beneficial in AD and related disorders."* P.358

AD = Atopic dermatitis; CI = Confidence interval; EASI = Eczema Area and Severity Index; HR = Hazard ratio; TWEL = Trans-epidermal water loss

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Malaysian Ministry of Health, 2018[10]	
"There was no reliable evidence to show that one emollient is more effective than another."(p.7)	Strength of evidence and recommendation not reported for this statement.
American Academy of Dermatology, 2014[11]	
"Head-to-head trials between specific moisturizing products are few in number, and those performed to date have not demonstrated one to be superior to others, including the PEDs." (p. 5)	Strength of evidence and recommendation not reported for this statement.

PEDs = Prescription emollient devices

Appendix 5: Additional References of Potential Interest

Seal of Acceptance Moisturizer in Combination with Corticosteroid Compared to Corticosteroid Alone - Cetaphil Restoraderm on one leg in combination with topical corticosteroid versus topical corticosteroid on other leg).

1. Simpson E, Dutronc Y. A new body moisturizer increases skin hydration and improves atopic dermatitis symptoms among children and adults. *J Drugs Dermatol.* 2011;10(7):744-749.

General Guidelines for Use of Emollients in Atopic (Not specific to emollients with Seal of Acceptance and without statements about product selection)

2. Chow S, Seow CS, Dizon MV, et al. A clinician's reference guide for the management of atopic dermatitis in Asians. Asia Pacific allergy. 2018 Oct;8(4):e41.

3. Kim JE, Kim HJ, Lew BL, et al. Consensus Guidelines for the Treatment of Atopic Dermatitis in Korea (Part I): General Management and Topical Treatment. *Annals of dermatology*. 2015 Oct;27(5):563-577. PubMed: PM26512171

4. 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. *J Eur Acad Dermatol Venereol*. 2018 May;32(5):657-682. PubMed: PM29676534