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Topical Antibiotics for Infected Dermatitis: A Review of the Clinical Effectiveness and Guidelines

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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.

Context and Policy Issues

Dermatitis, also referred as eczema, is a group of inflammatory skin diseases that occurs in both children and adults.[1] Dermatitis is characterized by itchiness, red skin, rash, sometimes with blisters, scaly skin lesions and fluid-filled bumps depending on the duration and severity of the disease.[1] Two common types of dermatitis are atopic dermatitis and contact dermatitis.[1] The latter can also be divided into two types: irritant contact dermatitis and allergic contact dermatitis.[1] Irritant dermatitis is caused by repeated exposure to substances that damage the skin, while allergic dermatitis occurs following brief contact with allergen, which triggers an immunologic reaction.[1] Atopic dermatitis is hereditary and the most common type of dermatitis. This condition generally starts in early childhood and may flare up throughout adulthood.[2] It affects about 17% of Canadians at some point in time and can have significant effect on quality of life of patients and family members.[1]

Most types of dermatitis required a combination of treatments and medications, including antihistamines, moisturizers, topical corticosteroids, topical calcineurin inhibitors, and phototherapy.[1] The skin barrier abnormalities in patients with dermatitis that are prone to penetration of infectious agents, most often is *Staphylococcus aureus*, which is found to colonize in approximately 90% of patients with atopic dermatitis.[3] The presence of bacteria may cause skin infection and may exacerbate the dermatitis conditions, and for that reason, it is believed that the use of antibiotics, either oral or topical form, to treat secondary skin infection may alleviate the severity of dermatitis.[4] It is, however, unclear if the treatment of skin infection by antibiotics is linked with the treatment of dermatitis.

The aim of this report is to review the clinical effectiveness and evidence-based guidelines on the use of topical antibiotics for treatment of infected dermatitis. The terms “eczema” and “dermatitis” are used interchangeably in this report.

Research Questions

1. What is the clinical effectiveness of topical antibiotics for patients with infected dermatitis?

2. What are the evidence-based guidelines regarding the use of topical antibiotics for the treatment of infected dermatitis?

Key Findings

Evidence to date suggests that topical antibiotics provide no additional benefits when added to other topical treatments in both children and adults with clinically infected dermatitis. The long-term or routine use of topical antibiotics for infected dermatitis is not recommended. The combination of intranasal mupirocin and bleach bath may be

recommended for patients with moderate to severe dermatitis who have signs of secondary bacterial infection.

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, randomized controlled trials, non-randomized 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, 2007 and January 31, 2017.

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 with infected dermatitis or secondarily infected dermatoses
Intervention	Topical Antibiotics: Polymyxin B sulfate-bacitracin (Polysporin ointment) Polymyxin B sulfate-gramicidin (Polysporin cream) Poymyxin B sulfate-bacitracin-gramicidin (Polysporin triple ointment) Bacitracin (Bacitin ointment) Mupirocin (Bactroban cream/ointment) Silver sufadiazine (Flamazine cream) Fusidic acid/fusidate sodium (Fucidin cream/ointment) Fusidic acid 2% plus hydrocortisone (Fucidin H)
Comparator	Placebo, topical antimicrobials compared to each other, oral antibiotics
Outcomes	Clinical effectiveness (e.g., symptom reduction), safety and harms, antimicrobial resistance, evidence-based guidelines.
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), or randomized controlled trials (RCTs)

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, and if they were published prior to 2007. Conference abstracts, duplicates of publication of the same study, or SRs, in which their included studies were overlapped with another SR published at a later date, were excluded.

Critical Appraisal of Individual Studies

The SIGN checklists were used to assess the quality of SRs and MAs,[5] and RCTs.[6] The Appraisal of Guidelines Research & Evaluation (AGREE II) instrument was used to evaluate the quality of the included guidelines.[7]

Summary of Evidence

Quantity of Research Available

A total of 129 citations were identified in the literature search. Following screening of titles and abstracts, 114 citations were excluded and 15 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 10 publications were excluded for various reasons, while nine publications, including two SRs, three RCTs and four guidelines, met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The characteristics of the SRs and MAs[8,9] and RCTs,[10-12] and guidelines[13-16] are summarized below and detailed in Appendix 2.

SRs and MAs

Study Design

One SR[8] included eight RCTs involving topical antibiotics for treatment of eczema with a total population of 1,012 patients. Another SR[9] included nine RCTs with a total population of 681 patients.

Country of Origin

Both SRs were conducted by authors from the UK[8,9] and were published in 2016[8] and 2008.[9]

Population

The overall populations of the included studies in both SRs[8,9] were mixed including patients with or without infected dermatitis. Patients of all ages (i.e., ≥6 months old) were included in the studied populations.[8,9] One SR[8] included patients of different types of dermatitis while the other[9] focused on atopic dermatitis. The mean age and gender were not explicitly reported.[8,9]

Interventions and Comparators

Most of the interventions in both SRs were a combination of topical antibiotics and topical steroids and the comparators were topical steroids alone. The topical antibiotics were fucidic acid, mupirocin, gentamycin, and tetracycline. The topical steroids included fluticasone, betamethasone, hydrocortisone, and triamcinolone. One SR[8] also included a study that compared a combination of topical antibiotic and tacrolimus (i.e., calcineurin inhibitor) with tacrolimus alone, and another study that compared the combination of mupirocin, which applied to nares of nose, and bleach bath with bleach bath alone.

Outcomes

The clinical outcomes included treatment response (i.e., proportion of patients had global clinical improvement rated by patients or medical practitioners), and global changes in subjective and objective composite rating scales (e.g., SCORing Atopic Dermatitis [SCORAD], Eczema Area and Severity Index [EASI], Six Area, Six Sign Atopic Dermatitis [SASSAD], Patient Oriented Eczema Measure [POEM], Atopic Dermatitis Area and Severity Index [ADASI], Leicester Sign Score [LSS], Inveestigator's Global Assessment of Disease Activity [IGADA], Three-Item Severity [TIS]).

Follow-up Period

The follow-up period of the included studies ranged from one to eight weeks in one SR[8] and from five to 28 days in the other SR.[9]

Data Analysis and Synthesis

No pooling of quantitative data was undertaken in one SR,[8] while meta-analysis approach was used to synthesize data in the other SR.[9] Risks of bias of the included studies were discussed along the presentation of the results,[8,9] and no subgroup or sensitivity analyses were performed.[9]

Quality Appraisal

The Cochrane risk of bias tool was used to assess the methodological quality of included studies, but the strength of evidence for each body of evidence was not assessed.[8,9]

RCTs

Study Design

Of the three included RCTs, two were double-blind placebo controlled[10,11] and one was an open-label active comparison.[12] Two RCTs recruited patients from multiple centres,[10,12] and one RCT enrolled patients from a single centre.[11]

Country of Origin

The RCTs were conducted in the UK,[10] USA,[11] and India,[12] and published in 2016,[10] 2014[11] and 2013,[12] respectively.

Population

One RCT[10] included children aged three months to less than eight years of age (mean age 3.1 years) who presented with clinically infected eczema (the ChildRen with Eczema, Antibiotic Management [CREAM] trial). The other two RCTs included adult patients (>18 years old) with moderate to severe hand and foot dermatitis[11] or with infected eczematous dermatosis.[12] It was unclear if patients with hand and foot dermatitis had infected or non-infected conditions.[11] The mean age and gender proportion reported in one RCT with adult patients was 43 years old and 38% male.[11]

Interventions and Comparators

The CREAM trial compared topical antibiotic (i.e., fusidic acid 2% cream) with placebo cream and oral antibiotic (i.e., flucloxacillin 50 mg/ml suspension) with placebo oral treatment.[10] All patients in this RCT received clobetasone butyrate 0.05% cream or

ointment for eczema on trunk or limb, or hydrocortisone 1% cream or ointment for eczema on face throughout the trial. The treatment period was seven days.

The RCT compared topical antibiotic (i.e., retapamulin 1% ointment) plus corticosteroid (i.e., clobetasol propionate 0.05% foam) with vehicle ointment placebo plus corticosteroid (i.e., clobetasol propionate 0.05% foam) in adult patients with hand and foot dermatitis.[11] Clobetasol was applied twice daily to hands or feet for two weeks followed by retapamulin or placebo ointment twice-daily application to anterior nares and the hands or feet for five consecutive days.

The RCT including adult patients with infected eczematous dermatosis compared the combination of antibiotic and steroid (i.e., cream of 2% fusidic acid and halometasone 0.05%) with another combination of antibiotic and steroid (i.e., cream of neomycin sulfate 0.5% and betamethasone 0.12%).[12] Patients with acute eczema were treated for 20 days, and those with chronic eczema were treated for 30 days.

Outcomes

The clinical outcomes included global changes in subjective and objective composite rating scales (e.g., POEM, EASI, IGADA, PSG [Pruritus Severity Grades]), dermatology-specific quality of life (e.g., Infant's Dermatitis Quality of Life Index [IDQoL], Children Dermatology Life Quality Index [CDLQI]), impact on family (e.g., Dermatitis Family Impact [DFI]), treatment response and adverse events.

Follow-up Period

In the CREAM trial, face-to-face follow-up visits were carried out at two weeks and four weeks after randomization.[10] At month 3, follow-up was conducted through mail and telephone call.[10] Follow-up visits were at day 6, day 5 and day 28 in the RCT having patients with hand and foot dermatitis,[11] and were at day 5, day 10, day 20 and day 30 in the other RCT including patients with infected eczematous dermatosis.[12]

Analysis

The evaluations of study endpoints in two RCTs[10,12] were performed on an intention-to-treat (ITT) basis, while analysis in one RCT[11] was performed on a per-protocol (PP) basis. One RCT[10] presented a sample size calculation to obtain sufficient power for the primary outcome, but the number of patients recruited and randomized did not reach that of the sample size calculation. One RCT[11] mentioned that sample size was determined, but did not provide any further details.

Guidelines

Country of Origin

Four evidence-based guidelines were identified: two were published in 2014,[13,14] one in 2011,[15] and one in 2008.[16] One guideline was from Europe (European Dermatology Forum [EDF]),[13] one from USA (American Academy of Dermatology [AAD]),[14] and two from UK (Scottish Intercollegiate Guideline Network [SIGN], National Institute for Health and Care Excellence [NICE]).[15,16]

Overall Objectives

The overall objectives of the included guidelines were to provide recommendations for the management and treatment of atopic dermatitis (atopic eczema) based on the existing evidence.

Target Users of the Guidelines

The guidelines were targeted to health care individuals including dermatologists, pediatricians, general practitioners, and all specialists involving in the care of patients suffering atopic dermatitis.

Methods Used to Formulate Recommendations

The strength of the recommendations in three guidelines[13-15] was graded according to the level of evidence in a hierarchical manner. One guideline[16] did not provide the grading of its recommendations.

Summary of Critical Appraisal

The summary of the quality assessment for the SRs, RCTs, and guidelines were briefly described below and presented in Appendix 3.

SRs and MAs

The SRs[8,9] were of high quality as most of the criteria were fulfilled, including an explicit research question, a comprehensive literature search, and at least two people were independently involved in the study selection and data extraction. Further, the status of publication was not used as an inclusion criterion and relevant study characteristics, quality assessment of included studies and a declaration of the conflicts of interest were completed. Appropriate methods of meta-analysis were used by one SR[9] but not applicable for the other,[8] which presented its findings through a narrative synthesis. None of the SRs were able to assess for publication bias as there were not enough studies. One SR[8] did not provided a list of excluded studies.

RCTs

One RCT[10] was of high quality as all criteria were fulfilled, including an explicit question, a detailed description of methodology on randomization, adequate method of concealment, blinding. As well, there was similarity between treatment groups, relevant outcome measures, an ITT analysis was conducted, and the trial was multi-centric. One RCT[12] was also of high quality as all the criteria were fulfilled, except that the method of concealment was not reported. One RCT[11] was of moderate quality as some criteria were not clearly reported or not fulfilled, such as the method of concealment, if an ITT analysis done, and whether the study was a multi-centric trial.

Guidelines

All guidelines[13-16] were explicit in terms of scope and purpose, clarity of presentation, and editorial independence. They were also explicit in the rigour of development, except that one guideline[13] did not explicitly describe a systematic method used to search for the evidence, the criteria for selecting the evidence, methods of formulating the recommendations, health benefits, side effects and risks considered in formulating the recommendations, and a procedure for updating the guidelines. Two

guidelines[13,14] did not meet all criteria for applicability of guidelines, including facilitators and barriers to its application, advice or tools on how the recommendations can be put into practice, resource implications, and monitoring or auditing criteria. Two guidelines[15,16] met all criteria for applicability, except for the resource implications.

Summary of Findings

Question 1: What is the clinical effectiveness of topical antibiotics for patients with infected dermatitis?

The main findings and conclusions of the included SRs and RCTs are presented in Appendix 4.

Global Changes in Composite Rating Scales for Eczema Severity

The findings from two SRs[8,9] and one RCT[10] showed that there were no statistically significant differences in global changes in composite rating scales (SCORAD, SASSAD, POEM, EASY) between topical antibiotics (i.e., fusidic acid, mupirocin, tetracycline, neomycin, flucloxacillin and gentamycin) plus corticosteroids (i.e., fluticasone, hydrocortisone, betamethasone, triamcinolone, clobetasone) and topical corticosteroids alone. Similar findings were observed with trial comparing fusidic acid plus tacrolimus versus tacrolimus alone, using the SCORAD score.[8] Topical antibiotics also showed no difference in POEM and EASI scores compared with oral antibiotics, judging from the point estimates and confidence intervals of both treatments.[10] However, the eczema severity was statistically and significantly reduced in patients treated with the combination of mupirocin, which was applied to nares of nose, and bleach bath compared with bleach bath alone, as assessed using the EASI score.[8] One RCT[12] found no difference in EASI scores between two different combinations of topical antibiotics and steroids (i.e., fusidic acid plus halomethasone versus neomycin plus betamethasone).

Treatment Response

There were no statistically significant differences in treatment response (i.e., proportion of patients who had improvement in symptoms or signs) between topical antibiotics (i.e., fusidic acid, mupirocin, gentamycin, retapamulin) plus corticosteroids (i.e., hydrocortisone, betamethasone, clobetasone) and corticosteroids alone at the end of treatment.[8,9,11] One RCT[12] found that there was no difference in the cure rate between two different combinations of topical antibiotics and steroids (i.e., fusidic acid plus halomethasone versus neomycin plus betamethasone). One RCT included in the SR[9] showed that the combination of neomycin and betamethasone was even inferior to clobetasol. The combination of topical steroid, antibiotic and antifungal (i.e., halcinonide, neomycin and nystatin) also showed no significant difference for the improvement in symptoms of eczema rated by patients or medical practitioners compared with topical steroid (i.e., hydrocortisone).[9]

Quality of Life and Family Impact

There were no statistically significant differences between the combination of topical antibiotic (fucidic acid) plus topical steroid (clobetasone) and clobetasone alone in quality of life of children assessed by either IDQoL or CDLQI.[10] Topical antibiotic (fusidic acid) also showed no difference in impact on family assessed by DFI

compared to control and to oral antibiotic (flucoxacillin).[10] The quality of life was not assessed in the SRs[8,9] or in the RCTs[11,12] involving adult patients.

Adverse Events

Adverse events were minor and not treatment related. No serious adverse events were detected that required withdrawal from treatment.

Question 2: What are the evidence-based guidelines regarding the use of topical antibiotics for the treatment of infected dermatitis?

The recommendations of the included guidelines[13-16] are presented in Appendix 4.

The EDF guideline[13] did not recommend long-term use of topical antibiotics for treatment of atopic eczema due to the risk of resistances and sensitizations.

The AAD guideline[14] did not recommend routine use of topical antibiotics in patients with atopic dermatitis for their lack of clinical helpfulness. The combination of intranasal mupirocin and bleach bath may be recommended for patients with moderate to severe dermatitis and having signs of secondary bacterial infection.

The SIGN guideline[15] did not provide any recommendations regarding the use of topical antibiotics for infected dermatitis due to poor evidence. However, it recognized that the combination of topical antibiotics and topical corticosteroids did not provide any clinical benefit in atopic eczema treatment compared to topical corticosteroid alone.

The NICE guideline[16] recommended that the use of topical antibiotics in children should be reserved for cases of infected atopic eczema and should not be used more than two weeks.

Limitations

Many RCTs included in the SRs were of high risk of bias based on the authors' quality assessment. Quality of reporting was generally limited as patient baseline characteristics were absent or poorly reported. The sample size was often not calculated to detect statistically significant difference of the primary endpoint. The treatment duration of many trials was up to two weeks. Heterogeneity existed among trials in terms of study population. For instance, they included patients of all ages, with different types of dermatitis, as well as participants with both clinically infected and non-infected dermatitis. The interventions and composite scoring systems for assessment of dermatitis severity were also different between studies. The degree of infection that had been clinically diagnosed was not clearly reported in the SRs[8,9] and RCTs,[11,12] making the evaluation of the applicability of the findings difficult. One recent RCT[10] involved children with mild clinically infected eczema, and thus, its findings could not be generalized to children with more severe infected eczema. All the identified guidelines[13-16] were for atopic dermatitis and not up to date, as the most recent ones were published in 2014.[13,14] Their recommendations were therefore not based on recent evidence, such as that of the CREAM trial.[10] No Canadian guidelines regarding the use of topical antibiotics for the treatment of infected dermatitis were identified.

Conclusions and Implications for Decision or Policy Making

The current evidence suggests that adding topical antibiotics to other topical treatments in people with clinically infected dermatitis provided no additional benefits. The use of intranasal mupirocin application and bleach bath may improve the severity of infected dermatitis. Three guidelines did not recommend the long-term or routine use of topical antibiotics in patients with atopic dermatitis, while another guideline could not make a recommendation because of the lack of clear evidence. Future studies should have a more formal definition of the term, “infected dermatitis”. There is a need for a large good quality study with long-term follow-up to determine when topical antibiotics should and should not be used in individuals with different types of dermatitis and different severity of infection.

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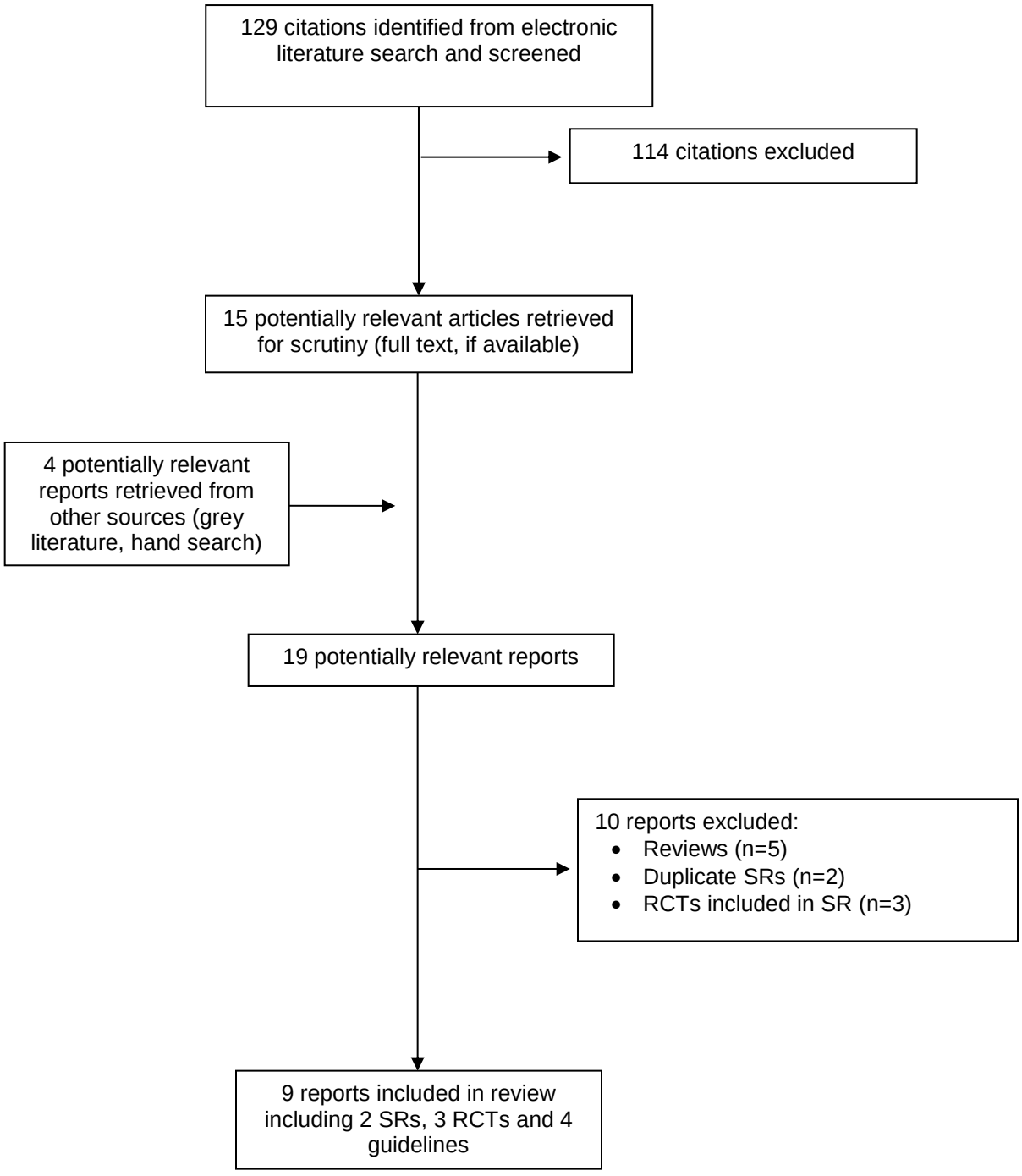
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table A1: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding	Types and Numbers of Primary Studies Included	Population Characteristics	Interventions	Comparators	Clinical Outcomes, Length of Follow-up
Nankervis et al., 2016[8] UK Funding: NIHR	SR of 8 RCTs related to topical antibiotics published between 2003 and 2012 Quality assessment using Cochrane risk of bias	1,012 patients of any age with definite or possible eczema (dermatitis); infected and non-infected Age: ≥6 months Gender: NR	Topical antibiotics (i.e., fusidic acid [3 RCTs], mupirocin [4 RCTs], tetracycline [1 RCT]) plus other topical treatments (i.e., tacrolimus, fluticasone, betamethasone, hydrocortisone, bleach bath, triamcinolone)	Other topical treatments alone (i.e., tacrolimus, fluticasone, betamethasone, hydrocortisone, bleach bath, triamcinolone)	• Changes in patient-rated symptoms of eczema (e.g., itching (pruritus), sleep loss) • Global changes in composite rating scales (i.e., SCORAD[a], EASI[b], SASSAD[c], POEM[d], ADASI[e], LSS[f], IGADA[g], TIS[h]) Follow-up: 1 to 8 weeks
Birnie et al., 2008[9] UK Funding: Queen Medical Centre NHS trust, UK	SR and MA of 9 RCTs (2 had no data of interest) published between 1976 and 2006 Quality assessment using Cochrane risk of bias	681 patients with atopic eczema (or atopic dermatitis) diagnosed by a dermatologist. Included both clinically infected and non-infected eczema Age: ≥2 years old in 3 trials; not stated in the remaining trials Gender: NR	Topical antibiotic + topical antifungal + topical steroid (1 RCT, n=4) Topical antibiotic + topical steroid (9 RCTs; n=677)	Topical steroids alone	• Global improvement in symptoms and/or signs (rated by patients or medical practitioners) • Severe AEs required treatment withdrawal • Minor AEs • Global changes in composite rating scales (i.e., SCORAD[a], EASI[b]) Follow-up: 5 to 28 days

ADASI = Atopic Dermatitis Area and Severity Index; EASI = Eczema Area and Severity Index; IGADA = Investigator's Global Assessment of Disease Activity; LSS = Leicester Sign Score; MA = meta-analysis; NHS = National Health Service; NIHR = National Institute for Health Research; NMIBC = non-muscle invasive bladder cancer; NIHR = National Institute for Health Research; NR = not reported; POEM = Patient Oriented Eczema Measure; RCT = randomized controlled trial; SASSAD = Six Area, Six Sign Atopic Dermatitis; SCORAD = SCORing Atopic Dermatitis; SR = systematic review; TIS = Three-Item Severity; UK = United Kingdom; vs = versus

[a] SCORAD (scale 0 to 103): Assessment of symptoms (i.e., pruritus, sleep disturbance) and sings (i.e., erythema, edema/induration/papulation, oozing/crusting/weeping/exudation, excoriation, lichenification, dryness)

[b] EASI (scale 0 to 72): Assessment of sings (i.e., erythema, edema/induration/papulation, excoriation, lichenification)

[c] SASSAD (scale 0 to 108): Assessment of sings (i.e., erythema, oozing/crusting/weeping/exudation, excoriation, lichenification, dryness, cracking/fissuring)

[d] POEM [scale 0 to 28]: Assessment of symptoms (i.e., pruritus, sleep disturbance) and sings (i.e., oozing/crusting/weeping/exudation, dryness, cracking/fissuring, flaking, bleeding)

[e] ADASI [scale 0 to 15]: Assessment of symptoms (i.e., pruritus) and sings (i.e., erythema, edema/induration/papulation, oozing/crusting/weeping/exudation, lichenification, scaling)

[f] LSS (scale 0 to 150): Assessment of sings (i.e., erythema, excoriation, lichenification, dryness, cracking/fissuring)

[g] IGADA (clear to very severe): Assessment of sings (i.e., erythema, edema/induration/papulation, oozing/crusting/weeping/exudation, excoriation, lichenification, scaling)

[h] TIS (scale 0 to 9): Assessment of sings (i.e., erythema, edema/induration/papulation, excoriation)

Table A2: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Study Name (if reported), Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes, Length of Follow-up
Francis et al., 2016[10] UK The CREAM study Funding: NIHR	DB, placebo-controlled RCT, multicenter, parallel, 1:1:1 ratio Analysis: ITT Sample size calculation: 75 patients per group were required to reach 90% power. Allowing 20% loss to follow-up, 94 patients was the recruitment target peer groups or 282 patients total for three groups. However, only 113 patients were enrolled and randomized into three groups.	Children (n=113) aged 3 months to <8 years of age who presented with clinically infected eczema were recruited from 33 general practitioner practices and dermatology clinic sites from 12 July 2013 to 28 November 2014 Mean age: 3.1 years Gender: 46% male, 54% female Duration of eczema flare: • 1 to 3 days: 12% • 4 to 7 days: 34% • 8 to 14 days: 28% • 15 to 28 days: 25% Over 90% had one or	Topical antibiotic (placebo oral treatment + fusidic acid 2% cream) (n=37) All patients received clobetasone butyrate 0.05% cream or ointment for eczema on trunk or limb, or hydrocortisone 1% cream or ointment for eczema on face through the trial Topical antibiotic or topical placebo was applied once daily for 14 days	Control (placebo oral treatment + placebo topical cream) (n=40) Oral antibiotic (flucloxacillin 50 mg/ml suspension + placebo topical cream) (n=36) All patients received clobetasone butyrate 0.05% cream or ointment for eczema on trunk or limb, or hydrocortisone 1% cream or ointment for eczema on face through the trial Oral antibiotic or oral placebo: 2.5 ml 4 times a day for 7 days (age 3 months to 2 years) or 5 ml four times a day for 7 days (2 years < age < 8 years)	• Subjective eczema severity (POEM[a]) • Objective eczema severity (EASI[b]) • Dermatology-specific quality of life (IDQoL[c] for children aged 3 months to <4 years; CDLQI[d] for children aged 4 years to <8 years) • Impact on family (DFI[e]) • Daily symptom scores[f] (diary completed daily by parents) Follow-up visit: Week 2 (face to face), Week 4 (face to face, 4-week dairy), Month 3 (telephone and postal follow-up)

First Author, Publication Year, Country, Study Name (if reported), Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes, Length of Follow-up
		more sign of infection (weeping, crusting, pustules or painful skin) 70% had *S. aureus* isolated from a skin swab			
Haddican et al., 2014[11] USA Funding: GlaxoSmithKline	DB, placebo-controlled RCT, single center, parallel, 1:1 ratio Analysis: PP (54 of 60 completed study) Sample size was determined to detect statistically significant difference; statistical details not provided	Patients (n=60) aged >18 years with moderate to very severe hand/foot dermatitis (assessed by PGA[g]) were recruited from a single centre from January 2012 to August 2012 Unclear if patients had infected or non-infected dermatitis Mean age: 43 years Gender: 38% male, 62% female Mean PGA (range): 3.6 (3 to 5)	Topical antibiotic (retapamulin 1% ointment) + corticosteroid (clobetasol propionate 0.05% foam) (n=30) Clobetasol was applied twice daily application to hands or feet for 2 weeks followed by retapamulin ointment twice-daily application to anterior nares and the hands or feet for five consecutive days	Placebo (vehicle ointment) + corticosteroid (clobetasol propionate 0.05% foam) (n=30) Clobetasol was applied twice daily application to hands or feet for 2 weeks followed by placebo ointment twice-daily application to anterior nares and the hands or feet for five consecutive days	• Proportion of patients with a PGA[g] of clear (0) or almost clear (1) • *S. aureus* carriage rates • *S. aureus* methicilline-resistance • *S. aureus* culture positive • Adverse events Follow-up visit: Day 6, Day 15, Day 28
Pratap et al., 2013[12] India Funding: Reddy's Laboratories Ltd	RCT, open-label, multicenter, parallel, 1:1 ratio Analysis: ITT No sample size	Patients (n=152) aged >18 years with infected eczematous dermatosis (acute or chronic) were recruited from multi centres (March 2009 to August 2009) Severity of eczema assessed by IGA[h]	Cream of fusidic acid 2% and halometasone 0.05% (n=77) Treatment duration: • Acute eczema: 20 days • Chronic eczema: 30 days	Cream of neomycin sulfate 0.5% and betamethasone 0.12% (n=75) Treatment duration: • Acute eczema: 20 days Chronic eczema: 30 days	• Change in eczema area and severity index score (EASI)[b] • Change in severity of eczema (IGA)[h] • Change in severity of pruritus (PSG)[i] • Treatment response[j] • Adverse events

First Author, Publication Year, Country, Study Name (if reported), Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes, Length of Follow-up
	calculation	Mean age: NR Gender: NR Just mentioned that there was no statistically significant difference between groups			Follow-up visit: • Acute eczema: Day 5, Day 10, Day 20 • Chronic eczema: Day 10, Day 20, Day 30

CDLQI = Children Dermatology Life Quality Index; CREAM = ChildRen with Eczema, Antibiotic Management; DB = double blind; DFI = Dermatitis Family Impact; EASI = Eczema Area and Severity Index; IDQoL = Infant's Dermatitis Quality of Life Index; IGA = Investigator's Global assessment; ITT = intention-to-treat; NIHR = National Institute for Health Research; NR = not reported; PGA = Physician Global Assessment; PSG = Pruritus Severity Grades; RCT = randomized controlled trial

[a] POEM (0 to 28): 0 to 2 = clear or almost clear; 3 to 7 = mild; 8 to 16 = moderate; 17 to 24 = severe; 25 to 28 = very severe

[b] EASI (0 to 72): 0 = clear; 0.1 to 1.0 = almost clear; 1.1 to 7.0 = mild; 7.1 to 21.0 = moderate; 21.1 to 50.0 = severe; 50.1 to 72.0 = very severe

[c] IDQoL (10 items; score range: 0 to 30): higher scores represent more severe (worse) impact on quality of life

[d] CDLQI (10 items; score range: 0 to 30): higher scores represent more severe (worse) impact on quality of life

[e] DFI (10 items, score range: 0 to 30): higher scores represent more severe (worse) impact on the family

[f] Daily symptom scores: Parents assessed overall severity of symptoms (itch, sleep disturbance, oozing or weeping, bleeding, fever, and adverse events [nausea, vomiting, diarrhea, abdominal pain, joint pain, new rash) using a severity scale of 0 to 6 (0 = normal/not affected; 6 = worse)

[g] PGA (0 to 5): 0 = clear (no inflammatory signs of atopic dermatitis); 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe

[h] IGA (0 to 3): 0 = clear or almost clear; 1 = mild; 2 = moderate; 3 = severe

[i] Pruritus Severity Grades (0 to 3): 0 = clear or almost clear; 1 = mild; 2 = moderate; 3 = severe

[j] Treatment response was defined as Cure, Improvement, and failure based on the IGA scores at the end of therapy

Table A3: Characteristics of Included Guidelines

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users/ Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
EDF[13] 2014 Europe	Intended users: Physicians including dermatologists, pediatricians, general practitioners and all	Therapeutic regimens on clinical entity, diagnosis or pathophysiology of the disease	Bacteria colonization, eczema severity, clinical improvement, and	Search for newer literature published after 2009 using Medline, EMBASE and the Cochrane	Recommendations were developed by a panel of content experts in Atopic Dermatitis	The guideline was externally reviewed by the European Dermatological

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users/ Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
Funding: Atopic Dermatitis Education Program (Schnupperchulung Deutschland)	specialists taking care of patients suffering from atopic eczema Also for patients and relatives to have reliable information and evaluation with regard to evidence-based therapeutic modalities Target population: Patients of all age with atopic dermatitis		safety	Library Synthesis based on evidence and expert consensus Evaluation was used the national standard Appraisal of Guidelines Research and Evaluation (AGREE).		Societies. The comments were internally reviewed by the guideline's authors
AAD[14] 2014 USA Funding: None	Intended users: Physicians involving in the management and treatment of atopic dermatitis Target population: Patients of all age with atopic dermatitis	Non-pharmacological and pharmacological interventions for the management and treatment of atopic dermatitis. Pharmacologic interventions included topical corticosteroids, topical calcineurin inhibitors, topical antimicrobials/antiseptics, topical antihistamines, and others (e.g., coal tar, phosphodiesterase inhibitors)	Clinical improvement, adverse events	Systematic search for evidence from major databases from November 2003 through November 2012 for clinical questions addressed in the previous version published in 2004 and from 1964 to 2012 for newly identified questions.	Recommendations were developed by a panel of content experts in Atopic Dermatitis	The guideline was developed in accordance with the American Academy of Dermatology (AAD)/AAD Association *Administrative Regulations for Evidence-based Clinical Practice Guidelines* (version approved May 2010)
SIGN[15] 2011 UK	Intended users: all healthcare professionals who manage patients with atopic eczema	Various topical treatments for atopic eczema, including emollients (moisturizers),	Bacteria colonization, clinical improvement	Systematic review of evidence from SRs and primary studies	Recommendations were developed by multidisciplinary groups of practicing clinicians	The guideline was developed using a standard methodology based on a

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users/ Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
Funding: NHS Quality Improvement Scotland	Target population: Patients of all age with atopic dermatitis	topical corticosteroids, topical calcineurin inhibitors and dressings), anti-infective treatments (such as antibiotics and antiseptics), antihistamines, complementary therapies and the role of diet and environmental factors				systematic review of evidence (i.e., "SIGN 50: A guideline Developer's Handbook", available at www.sign.ac.uk)
NICE[16] 2007 UK Funding: NICE	Intended users: all healthcare professionals involving in the care of children with atopic eczema, those responsible for commissioning and planning healthcare services, and families and other caregivers of children with atopic eczema Target population: Children from birth to age of 12 years	Providing guidance on diagnosis and assessment of the impact of the condition, management during and between flares, and information and education to children and their families/caregivers about the condition	Bacteria colonization, eczema severity, clinical improvement, and safety	Systematic review of evidence from SRs and primary studies	Recommendations were developed a panel of dermatologists, nurses, general practitioners, pediatrician, pharmacists, and patient caregiver representatives	The guideline was developed in accordance with the NICE guideline development process outlines in the 2005 technical manual and the 2006 and 2007 editions of the *Guidelines Manual*.

AAD = American Academy of Dermatology; EDF = European Dermatology Forum; NICE = National Institute for Health and Care Excellence; RCTs = randomized controlled trials; SIGN = Scottish Intercollegiate Guidelines Network

Table A4: Grade of Recommendations and Level of Evidence

Guideline Society or Institute, Year, Country	Grade of Recommendation	Level of Evidence
EDF[13] 2014 Europe	**A** 1a, 1b **B** 2a, 2b, 3a, 3b **C** 4 **D** Expert opinion	**1a** Meta-analysis of randomized clinical trials (RCT) **1b** Single RCTs **2a** Systematic review of cohort studies **2b** Single cohort studies and RCTs of limited quality **3a** Systematic review of case control studies **3b** Single case control study **4** Case series, case cohort studies or cohort studies of limited quality
AAD[14] 2014 USA	**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	**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)
SIGN[15] 2011 UK	**A** At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results **B** A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+ **C** A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++ **D** Evidence of level 3 or 4; or extrapolated evidence from studies rated as 2+ **GPP** Recommended best practice based on the clinical experience of the guideline development group	**1++** High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias **1+** Well-conducted meta-analysis, systematic reviews, or RCTs with a low risk of bias **1-** Meta-analyses, systematic reviews, or RCTs with a high risk of bias **2++** High quality systematic reviews of case control or cohort studies; high quality case control or cohort studies with very low risk of confounding or bias and a high probability that the relationship is causal **2+** Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal **2-** Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal **3** Non-analytic studies, e.g., case reports, case series

Guideline Society or Institute, Year, Country	Grade of Recommendation	Level of Evidence
		4 Expert opinion
NICE[16] 2007 UK	None	**1++** High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias **1+** Well-conducted meta-analysis, systematic reviews, or RCTs with a low risk of bias **1-** Meta-analyses, systematic reviews, or RCTs with a high risk of bias **2++** High quality systematic reviews of case control or cohort studies; high quality case control or cohort studies with very low risk of confounding or bias and a high probability that the relationship is causal **2+** Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal **2-** Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal **3** Non-analytic studies, e.g., case reports, case series **4** Expert opinion

AAD = American Academy of Dermatology; EDF = European Dermatology Forum; NICE = National Institute for Health and Care Excellence; RCTs = randomized controlled trials; SIGN = Scottish Intercollegiate Guidelines Network

Appendix 3: Quality Assessment of Included Studies

Table A5: Quality Assessment of Systematic Reviews

SIGN Checklist: Internal Validity	Nankervis et al., 2016[8]	Birnie et al., 2008[9]
1. The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper	Yes	Yes
2. A comprehensive literature search is carried out	Yes	Yes
3. At least two people should have selected studies	Yes	Yes
4. At least two people should have extracted data	Yes	Yes
5. The status of publication was not used as an inclusion criteria	Yes	Yes
6. The excluded studies are listed	No	Yes
7. The relevant characteristics of the included studies are provided	Yes	Yes
8. The scientific quality of the included studies was assessed and reported	Yes	Yes
9. Was the scientific quality of the included studies used appropriately?	Yes	Yes
10. Appropriate methods are used to combine the individual study findings	NA	Yes
11. The likelihood of publication bias was assessed appropriately	NA	NA
12. Conflicts of interest are declared	Yes	Yes
Overall Assessment of the Study		
High, Moderate, Low	High	High

For overall assessment of the study: *High* indicated that all or most criteria have been fulfilled; where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter. *Moderate* indicates that some of the criteria have been fulfilled; those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. *Low* indicates that few or no criteria fulfilled; the conclusions of the study are thought likely or very likely to alter.

Table A6: Quality Assessment of Primary Studies

SIGN Checklist: Internal Validity	Francis et al., 2016[10]	Haddican et al., 2014[11]	Pratap et al., 2013[12]
1. The study addresses an appropriate and clearly focused question.	Yes	Yes	Yes
2. The assignment of subjects to treatment groups is randomized.	Yes	Yes	Yes
3. An adequate concealment method is used.	Yes	Can't tell	Can't tell
4. Subjects and investigators are kept 'blind' about treatment allocation.	Yes	Yes	Yes
5. The treatment and control groups are similar at the start of trial.	Yes	Yes	Yes
6. The only difference between groups is the treatment under investigation.	Yes	Yes	Yes
7. All relevant outcomes are measured in a standard, valid and reliable way.	Yes	Yes	Yes

SIGN Checklist: Internal Validity	Francis et al., 2016[10]	Haddican et al., 2014[11]	Pratap et al., 2013[12]
8. What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	Control: 37% Oral antibiotic: 22% Topical antibiotic: 43%	10% total	14% per group
9. All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes	No	Yes
10. Where the study is carried out more than one site, results are comparable for all sites.	Yes	No	Yes
Overall Assessment of the Study			
High, Moderate, Low	High	Moderate	High

For overall assessment of the study: *High* indicated that all or most criteria have been fulfilled; where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter. *Moderate* indicates that some of the criteria have been fulfilled; those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. *Low* indicates that few or no criteria fulfilled; the conclusions of the study are thought likely or very likely to alter.

Table A7: Quality Assessment of Guidelines

AGREE II Checklist	EDF, 2014[13]	AAD, 2014[14]	SIGN, 2011[15]	NICE, 2007[16]
Scope and purpose				
1. Objectives and target patients population were explicit	Yes	Yes	Yes	Yes
2. The health question covered by the guidelines is specifically described	Yes	Yes	Yes	Yes
3. The population to whom the guidelines is meant to apply is specifically described	Yes	Yes	Yes	Yes
Stakeholder involvement				
4. The guideline development group includes individuals from all relevant professional groups	Yes	Yes	Yes	Yes
5. The views and preferences of the target population have been sought	Yes	Yes	No clear	Yes
6. The target users of the guideline are clearly defined	Yes	Yes	Yes	Yes
Rigour of development				
7. Systematic methods were used to search for evidence	Not clear	Yes	Yes	Yes
8. The criteria for selecting the evidence are clearly described	Not clear	Yes	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described	Yes	Yes	Yes	Yes
10. The methods of formulating the recommendations are clearly described	Not clear	Yes	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations	Not clear	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence	Yes	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its	Yes	Yes	Yes	Yes

AGREE II Checklist	EDF, 2014[13]	AAD, 2014[14]	SIGN, 2011[15]	NICE, 2007[16]
publication				
14. A procedure for updating the guideline is provided	Not clear	Yes	Yes	Yes
Clarity of presentation				
15. The recommendations are specific and unambiguous	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented	Yes	Yes	Yes	Yes
17. Key recommendations are easily identified	Yes	Yes	Yes	Yes
Applicability				
18. The guideline describes facilitators and barriers to its application	Not clear	Not clear	Yes	Yes
19. The guidelines provides advice and/or tools on how the recommendations can be put into practice	Not clear	Not clear	Yes	Yes
20. The potential resource (cost) implications of applying the recommendations have been considered	Not clear	Not clear	Not clear	Not clear
21. The guideline presents monitoring and/or auditing criteria	Not clear	Not clear	Yes	Yes
Editorial independence				
22. The views of the funding body have not influenced the content of the guideline	Yes	Yes	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed	Yes	Yes	Yes	Yes

Appendix 4: Main Study Findings and Author's Conclusions

Table A8: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusions
Nankervis et al., 2016[8]	
Topical Fusidic acid (3 RCTs) Risk of bias: high Efficacy Eczema severity and treatment success • Fusidic acid + tacrolimus vs tacrolimus: SCORAD scores, NS (p=0.81) after 2 weeks • Fusidic acid + fluticasone vs fluticasone: TSS: 82.9% vs 82.7% had clinical improvement (treatment success) after 2 weeks and 8 weeks; NS difference; p=0.81 • Fusidic acid + fluticasone vs vehicle preparation (placebo): TSS: 82.9% vs 33.0% had clinical improvement (treatment success) after 2 weeks and 8 weeks; p<0.001 • Fucidic acid + betamethasone vs mupirocin + betamethasone: similar clinical improvement after 2 weeks (using a scoring system of Costa and colleagues [scoring 0 to 6 for erythema, edema, vesicles, exudation, crusts, excoriation, scale, and lichenification; maximum score of 98]) Harms Minor skin irritation, presence of fusidic-acid resistant strain on skin of some patients. Topical mupirocin (4 RCTs) Risk of bias: high Efficacy Eczema severity and treatment success • Mupirocin + hydrocortisone vs hydrocortisone: EASI scores; NS difference (p>0.05) after 28 days • Fucidic acid + betamethasone vs mupirocin + betamethasone: similar clinical improvement • Mupirocin + hydrocortisone vs hydrocortisone: SCORAD and EASI: 74% vs 65% had improvement (treatment success) after 7 days; NS difference • Mupirocin + hydrocortisone vs emollient: SCORAD and EASI: 74% vs 36% had improvement (treatment success) after 7 days; p=0.012 • Mupirocin (applied to nares of nose) + bleach bath vs bleach bath: EASI scores, significant reduction at 1 and 3 months, p=0.004 Harms Minor skin irritation, no information about adverse events Topical tetracycline (1 RCT) Risk of bias: low Efficacy Eczema severity - Tetracycline + triamcinolone vs triamcinolone: SCORAD and SASSAD scores, NS difference between treatments after 2 weeks and 6-week maintenance period Harms Low to moderate level of folliculitis in both groups	- *"For clinically infected eczema, there is currently no evidence of additional benefit from adding fusidic acid to other topical treatments over adding mupirocin. For non-infected eczema, there is no evidence of benefit from adding fusidic acid to short-term topical corticosteroid treatment"*[8] p.91, 92 - *"No evidence of benefit for addition of antibiotics (mupirocin) to steroid treatment for non-infected eczema"*[8] p.93 - *"The use of dilute bleach baths and intranasal mupirocin application resulted in a significant improvement in eczema severity"*[8] p.97 - *"There is fairly well-reported trial did not find any benefit of adding tetracycline to topical corticosteroid treatment in people with eczema without overt signs of clinical infection"*[8] p.95
Birnie et al., 2008[9]	
1) Topical steroid + antibiotic and antifungal vs topical steroid Risk of bias: high (1 RCT; n=4)	"*There was no clear evidence that widely used topical steroid/antibiotic*

Main Study Findings	Author's Conclusions
Efficacy - Global outcome (i.e., improvement in symptoms and/or signs as rated by patient or medical practitioner) Halcinonide + neomycin + nystatin vs hydrocortisone: NS difference 2) Topical corticosteroids + antibiotics vs corticosteroids Risk of bias: high (9 RCTs; n=677) Efficacy - Global outcome: Betamethasone + gentamycin cream vs betamethasone cream: NS difference; RR 0.31; 95% CI 0.07 to 1.35 Betamethasone + neomycin cream vs super-potent clobetasol: Significant improvement in favor of clobetasol; MD 1.2; 95% CI 0.25 to 2.15 - Global changes in composite rating scales: Triamcinolone + tetracycline vs triamcinolone: NS difference in SCORAD scores; MD -0.40; 95% CI -10.39 to 9.59 Hydrocortisone + mupirocin vs hydrocortisone: NS difference in EASI scores; MD -1.08; 95% CI -2.51 to 0.35 Adverse events - Serious, requiring withdrawal from treatment: NS difference; RR 0.49; 95% CI 0.09 to 2.78 - Minor; not requiring withdrawal from treatment: Fewer in combination treatment group compared to the control; RR 0.34; 95% CI 0.15 to 0.77	*combinations were any better than topical steroids used alone"*[9] p.2

CI = confidence interval; DFI = Dermatitis Family Impact; EASI = Eczema Area and Severity Index; MA = meta-analysis; MCID = minimal clinically important difference; MD = mean difference; NS = not statistically significant; RCT = randomized controlled trial; RR = relative risk; SASSAD = Six Area, Six Sign Atopic Dermatitis; SCORAD = SCORing Atopic Dermatitis; SD = standard deviation; SR = systematic review; TSS = total severity score; vs = versus

Table A9: Summary of Findings of Included Primary Studies

Main Study Findings | **Author's Conclusions**

Francis et al. (CREAM study), 2016[10]

Effect of oral and topical antibiotics on subjective and objective eczema severity, family impact and quality of life		
Outcome	Topical antibiotic vs control	Oral antibiotic vs control
	Intervention effect; MD (95% CI)	
POEM (subjective)		
2 weeks	1.49 (-1.55 to 4.53)	1.52 (-1.35 to 4.40)
4 weeks	0.00 (-3.07 to 3.07)	-0.18 (-3.10 to 2.75)
3 months	-1.13 (-4.32 to 2.06)	-0.21 (-3.12 to 2.70)
Topical and oral antibiotics had non-statistically higher (worse severity) POEM scores differences from control. MCID for POEM is 3.4		
EASI (objective)		
2 weeks	0.42 (0.09 to 0.75)	0.20 (-0.12 to 0.52)
4 weeks	0.02 (-0.34 to 0.38)	-0.13 (-0.47 to 0.22)
Topical antibiotics had unimportant clinical effect at 2 weeks and oral antibiotics non-statistically higher (worse severity) EASI scores differences from control. MCID for EASI is 6.6		
DFI		
2 weeks	0.21 (-0.15 to 0.58)	0.17 (-0.18 to 0.53)
4 weeks	-0.00 (-0.43 to -0.42)	-0.02 (-0.43 to 0.39)

"Our results provide the clearest evidence to date that neither topical nor oral antibiotics are likely to benefit children with mild clinically infected eczema"[10] p.62

Main Study Findings			Author's Conclusions
3 months	-0.01 (-0.57 to 0.55)	-0.04 (-0.56 to 0.49)	
Topical and oral antibiotics showed no difference in impact on family compared to control. All estimates of effect were close to null.			
IDQoL			
2 weeks	0.18 (-0.03 to 0.40)	0.11 (-0.10 to 0.32)	
4 weeks	0.05 (-0.20 to 0.30)	-0.04 (-0.28 to 0.21)	
3 months	-0.07 (-0.31 to 0.17)	-0.21 (-0.44 to 0.02)	
No significant intervention effects in quality of life			
CDLQI			
2 weeks	0.70 (0.12 to 1.28)	0.43 (-0.16 to 1.02)	
4 weeks	-0.17 (-0.87 to 0.53)	-0.15 (-0.84 to 0.54)	
3 months	-0.13 (-0.96 to 0.70)	-0.14 (-0.97 to 0.70)	
No significant intervention effects in quality of life			
Haddican et al., 2014[11]			
Efficacy Proportion of patients with a PGA of clear (0) or almost clear (1) At day 15, 73% (Retapamulin + clobetasol) vs 47% (clobetasol), *p*=0.04 At day 28, 50% (Retapamulin + clobetasol) vs 37% (clobetasol), *p*=0.28 Adverse events Urinary tract infection (n=1), upper respiratory infection (n=3), eczema flare (n=2), dryness (n=1), and pruritus (n=1). None related to study drug			*"At Day 15, retapamulin 1% ointment with clobetasol propionate 0.05% foam was more efficacious than vehicle ointment and clobetasol propionate 0.05% foam for disease improvement…in adult subjects with hand/foot dermatitis"*[11] p.32
Pratap et al., 2013[12]			
Halomethasone + fusidic acid vs betamethasone + neomycin Efficacy at end of treatment - Change in eczema area and severity index score (EASI): Mean +/- SD: 0.83 +/- 0.78 vs 1.05 +/- 1.32; *p*=0.24 - Change in severity of eczema (IGA): Mean +/- SD: 2.43 +/- 2.73 vs 2.53 +/- 0.80; *p*=0.64 - Change in severity of pruritus (PSG): Mean change: 0.60 vs 0.67 - Treatment response Cure: 54% vs 50% Adverse events - Serious: none - Others: 3 patients (hypopigmentation, dissemination) in halomethasone + fusidic acid group and 2 patients (ulcer, autosensitization) in betamethasone + neomycin group - Withdrawal due to adverse events: 1 patient in halomethasone + fusidic acid group and 2 patients in betamethasone + neomycin group			*"Combination of halomethasone 0.05% and fusidic acid 2% cream is effective and well tolerated in the treatment of both acute and chronic infected eczema with a comparable efficacy to betamethasone 0.12% and neomycin sulfate 0.5% cream."*[12] p.5

CDLQI = Children Dermatology Life Quality Index; CI = confidence interval; CREAM = ChildRen with Eczema, Antibiotic Management; DFI = Dermatitis Family Impact; EASI = Eczema Area and Severity Index; IDQoL = Infant's Dermatitis Quality of Life Index; MCID = minimal clinically important difference; MD = mean difference; NS = not statistically significant; PGA = Physician Global Assessment; POEM = Patient Oriented Eczema Measure; PSG = Pruritus Severity Grades; RCT = randomized controlled trial; RR = relative risk; SASSAD = Six Area, Six Sign Atopic Dermatitis; SCORAD = SCORing Atopic Dermatitis; SD = standard deviation; SR = systematic review; TSS = total severity score; vs = versus

Table A10: Summary of Findings of Included Guidelines

Recommendations
EDF, 2014[13]
• Recommendation: *"The long term application of topical antibiotics is not recommended due to the risk of increasing resistances and sensitizations (the latter being relevant for a subgroup of topical antibiotics only) (-, D)"*[13] p.27
AAD, 2014[14]
• Recommendation: *"Except for bleach baths with intranasal mupirocin, no topical antistaphyloccocal treatment has been shown to be clinically helpful in patients with atopic dermatitis, and is not routinely recommended. (I, A)"*[14] p.32 • Recommendation: "*In patients with moderate to severe atopic dermatitis and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity. (II, B)"*[14] p.32
SIGN, 2011[15]
• Recommendation: No recommendations provided However, the guideline stated: *"Although, in some studies, they are associated with reduction in S. aureus colonization, a systematic review found no clear evidence that topical antibiotics combined with topical corticosteroids provided clinical benefit in atopic eczema treatment compared to topical corticosteroids alone. Overall methodological quality of trials was poor and it is not possible to provide an evidence based recommendation for practice. (1^{++})"*[15] p.15
NICE, 2007[16]
• Recommendation: *"The use of topical antibiotics in children with atopic eczema, including those combined with topical corticosteroids, should be reserved for cases of clinical infection in localized areas and used for no longer than 2 weeks"*[16] p.24

AAD = American Academy of Dermatology; AD = atopic dermatitis; EDF = European Dermatology Forum; NICE = National Institute for Health and Care Excellence; SIGN = Scottish Intercollegiate Guidelines Network