Ann Allergy Asthma Immunol 000 (2022) 1–9

Contents lists available at ScienceDirect

Bleach baths for atopic dermatitis

A systematic review and meta-analysis including unpublished data, Bayesian interpretation, and GRADE

Layla Bakaa, OSSD[*]; Jeffrey M. Pernica, MSc, MD, FRCPC, DTMH[†]; Rachel J. Couban, MISt[‡]; Kelly Jo Tackett, MPH[§]; Craig N. Burkhart, MD, MS, MPH[§]; Liz Leins, RN, PgDipACN(Paed), MN[‖]; Joanne Smart, MD, PHD[‖]; Maria Teresa Garcia-Romero, MD, MPH[¶]; Itzel Guadalupe Elizalde-Jiménez, MD[¶,#]; Michael Herd, BSc, MBChB, Dip Paed, FRACP[**,¶¶¶¶]; Rachel Netahe Asiniwasis, MD, FRCPC[††]; Mark Boguniewicz, MD[‡‡]; Anna De Benedetto, MD[§§]; Lina Chen, BSc[‖‖]; Kathy Ellison, MEd[¶¶]; Winfred Frazier, MD, MPH[##]; Matthew Greenhawt, MD, MBA, MSc[***]; Joey Huynh, MPT[†††]; Jennifer LeBovidge, PhD[‡‡‡]; Mary Laura Lind, PhD[§§§]; Peter Lio, MD[‖‖‖]; Monica O'Brien, MBS[¶¶¶]; Peck Y. Ong, MD[###]; Jonathan I. Silverberg, MD, PhD, MPH[****]; Jonathan M. Spergel, MD, PhD[††††]; Julie Wang, MD[‡‡‡‡]; Wendy Smith Begolka, MBD[§§§§]; Lynda Schneider, MD, PhD, FRCPC[‡‡‡]; Derek K. Chu, MD, PhD, FRCPC[*,‡,‖‖‖‖]

[*] *Evidence in Allergy Group, Department of Medicine, McMaster University, Hamilton, Ontario, Canada*
[†] *Department of Pediatrics, Division of Infectious Diseases, McMaster University, Hamilton, Ontario, Canada*
[‡] *Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada*
[§] *Department of Dermatology, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina*
[‖] *Royal Children's Hospital, Allergy & Immunology, Victoria, Australia*
[¶] *Department of Dermatology, National Institute of Pediatrics, Mexico City, Mexico*
[#] *Ministry of Health, General Directorate of Quality and Education of Health, Mexico City, Mexico*
[**] *Paediatric Department, Waitakere Hospital, Waitemata District Health Board, Auckland, New Zealand*
[††] *Origins Dermatology Centre, University of Saskatchewan, Regina, Saskatchewan, Canada*
[‡‡] *National Jewish Health, Denver, Colorado*

Reprints: Derek K. Chu, MD, PhD, FRCPC, Division of Clinical Immunology & Allergy, Department of Medicine and Department of Health Research Methods, Evidence and Impact, McMaster University, Room 3V51 McMaster University Medical Centre, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada; E-mail: chudk@mcmaster.ca.

Disclosures: Dr. De Benedetto is an investigator for Dermira, Kiniksa, Novartis, and Pfizer and a consultant for dMed Biopharmaceutical Co, Ltd. Dr. Boguniewicz conducts research at Regeneron and Incyte; and is part of advisory boards and consults for AbbVie, Janssen, LEO Pharma, Lilly, Pfizer, Regeneron, and Sanofi Genzyme. Ms. Begolka declares receiving research grants from Pfizer; is on the advisory board for Incyte and Pfizer; received honoraria from Incyte and Pfizer; and is a principal investigator for Pfizer. Dr. Greenhawt is a consultant for Aquestive; a member of physician and medical advisory boards for DBV Technologies, Sanofi/Regeneron, Genentech, Nutricia, Novartis, Acquestive, Allergy Therapeutics, Pfizer, US World Meds, Allergenis, Aravax, and Prota; a member of the Scientific Advisory Council for the National Peanut Board; the senior associate editor for the *Annals of Allergy, Asthma & Immunology*; a member of the Joint Taskforce on Allergy Practice Parameters; and has received honorarium for lectures from ImSci, the Allergy and Asthma Foundation of America, and the MedLearningGroup. Dr. Garcia-Romero has received honoraria as a speaker from Pierre Fabre and Sanofi; and has served on an advisory board for Pfizer. Dr. Lind is the co-founder of Sequitur Health Corporation. Dr. Lio reports receiving research grants/funding from the National Eczema Association, AOBiome, Regeneron/Sanofi Genzyme, and AbbVie; is on the speaker's bureau for Regeneron/Sanofi Genzyme, Pfizer, Incyte, Eli Lilly, LEO, Galderma, and L'Oreal; reports serving on the consulting/advisory boards for Almirall, ASLAN Pharmaceuticals, Concerto Biosciences, Dermavant, Regeneron/Sanofi Genzyme, Pfizer, LEO Pharmaceuticals, AbbVie, Eli Lilly, Micreos, L'Oreal, Pierre-Fabre, Johnson & Johnson, Level Ex, KPAway, Unilever, Menlo Therapeutics, Theraplex, IntraDerm, Exeltis, AOBiome, Realm Therapeutics, Altus Labs, Galderma, Verrica, Arbonne, Amyris, Bodewell, Burt's Bees, My-Or Diagnostics, and Kimberly-Clark; has a patent pending for a Theraplex product with royalties paid; is a board member and scientific advisory committee member of the National Eczema Association; an investor at LearnSkin; and has stock options with Micreos, Altus Labs, Boston Skin Science, and Concerto Biosciences. Dr. Ong is a consultant for Regeneron, Sanofi, Janssen, Incyte, and AbbVie. Dr. Pernica reports receiving a grant from MedImmune. Dr. Spergel declares receiving grants or contracts from Novartis, Abbott, Regeneron, Sanofi, and the National Institutes of Health; receiving royalties or licenses from UpToDate; receiving consulting fees from Regeneron, Sanofi, Novartis, Takeda, Allakos, and Alladapt; receiving payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Medscape and Rockpointe; and being on the Safety Monitoring Board or Advisory Board of the National Institute of Allergy and Infectious Disease and of Syneos. Dr. Schneider is on the Medical Advisory Board for Food Allergy Research and Education and the Data and Safety Monitoring Board for Alladapt; and an investigator for DBV Technologies and Regeneron. Dr. Wang reports receiving institutional research funding from Regeneron, DBV, and Aimmune; consultancy fees from DBV, ALK Abello, and Genentech; being an UpToDate author; and being a member of Joint Task Force on Practice Parameters. All other authors declare no conflict of interest.

Funding: This work receives funding from the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology.

Role of the Funding Source: The American College of Allergy, Asthma & Immunology and the American Academy of Allergy, Asthma & Immunology commissioned this review through the Joint Task Force on Practice Parameters to inform upcoming guidance on management of atopic dermatitis. The funder contributed to defining the scope of the review but otherwise had no role in study design and data collection. After agreeing to the initial scope of the project, the funder did not have any input in the interpretation of the data, drafting of the manuscript, and submission of the report. The funder received a copy of the manuscript at time of submission. The review team had the ability, but not obligation, to consider the funder's feedback. The first and corresponding authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

https://doi.org/10.1016/j.anai.2022.03.024

§§ University of Rochester Medical Center, Rochester, New York
|||| University of Ottawa, Ottawa, Ontario, Canada
¶¶ Westerville, Ohio
Department of Family Medicine, UPMC St. Margaret, Pittsburgh, Pennsylvania
*** Section of Allergy and Immunology, Children's Hospital Colorado, Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado
††† Orthopedic Neurological Rehabilitation, Northridge, California
‡‡‡ Division of Immunology, Boston Children's Hospital, Boston, Massachusetts
§§§ School for Engineering of Matter, Transport and Energy, Arizona State University, Tempe, Arizona
|||| Northwestern University Feinberg School of Medicine, Chicago, Illinois
¶¶¶ Tufts University School of Medicine, Boston, Massachusetts. Medical Student, Class of 2025
Children's Hospital Los Angeles, USC Keck School of Medicine, Los Angeles, California
**** Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC
†††† Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania and Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
‡‡‡‡ Icahn School of Medicine at Mount Sinai, New York City, New York
§§§§ National Eczema Association, Novato, California
||||| The Research Institute of St. Joe's Hamilton, Hamilton, Ontario, Canada
¶¶¶¶ Current location: Paediatric Department, Whakatane Hospital Bay of Plenty District Health Board, Whakatane, New Zealand

ARTICLE INFO

Article history:
Received for publication January 6, 2022.
Received in revised form March 22, 2022.
Accepted for publication March 24, 2022.

ABSTRACT

Background: Bleach bathing is frequently recommended to treat atopic dermatitis (AD), but its efficacy and safety are uncertain.
Objective: To systematically synthesize randomized controlled trials (RCTs) addressing bleach baths for AD.
Methods: We searched MEDLINE, EMBASE, CENTRAL, and GREAT from inception to December 29, 2021, for RCTs assigning patients with AD to bleach vs no bleach baths. Paired reviewers independently and in duplicate screened records, extracted data, and assessed risk of bias (Cochrane version 2) and GRADE quality of evidence. We obtained unpublished data, harmonized individual patient data and did Frequentist and Bayesian random-effects meta-analyses.
Results: There were 10 RCTs that enrolled 307 participants (median of mean age 7.2 years, Eczema Area Severity Index baseline mean of means 27.57 [median SD, 10.74]) for a median of 6 weeks (range, 4-10). We confirmed that other trials registered globally were terminated. Bleach baths probably improve AD severity (22% vs 32% improved Eczema Area Severity Index by 50% [ratio of means 0.78, 95% credible interval 0.59-0.99]; moderate certainty) and may slightly reduce skin *Staphylococcal aureus* colonization (risk ratio, 0.89 [95% confidence interval, 0.73-1.09]; low certainty). Adverse events, mostly dry skin and irritation, along with itch, patient-reported disease severity, sleep quality, quality of life, and risk of AD flares were not clearly different between groups and of low to very low certainty.
Conclusion: In patients with moderate-to-severe AD, bleach baths probably improve clinician-reported severity by a relative 22%. One in 10 will likely improve severity by 50%. Changes in other patient-important outcomes are uncertain. These findings support optimal eczema care and the need for additional large clinical trials.
Trial Registration: PROSPERO Identifier: CRD42021238486.

Introduction

Atopic dermatitis (AD; typically referred to as eczema or atopic eczema)[1] affects up to 13.0% of children and 4.9% of adults worldwide.[2,3] It typically starts in infancy, is characterized by dry, inflamed, and itchy skin, and is often complicated by sleep disturbance, impaired quality of life,[4-6] and skin infections.

Bathing in dilute bleach (sodium hypochlorite; NaOCl) is a common adjunctive treatment for AD. Administration of this treatment includes 1/4 to 1/2 cup of 5% to 6% bleach in a full bathtub (approximately 40 gallons of water) for a final concentration approximately 0.005%, applied for 10 minutes, 2 to 3 times per week.[7,8] Bleach's antiseptic properties, recognized since the 18th century as a treatment of battlefield wounds,[9] are hypothesized to improve AD severity by decreasing the *Staphylococcus aureus* (*S aureus*) bacteria that typically colonizes AD skin lesions,[10,11] without risk of bacterial resistance.[12,13] Bleach concentrations recommended for AD, however, have been reported to not be antistaphylococcal in vitro[14] and may directly exert beneficial anti-inflammatory effects on eczematous skin independent of their antistaphylococcal effects.[15]

Despite the common use of bleach baths to treat AD, evidence regarding efficacy and safety is unclear. There were 3 systematic reviews[13,16,17] that narratively synthesized observational data along with 5 randomized controlled trials (RCTs) and were uncertain whether they provided added benefit above usual bathing practices with water only. The American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology thus identified the practice of bleach baths as a priority to clarify for its upcoming practice parameter guideline update.[8] We systematically reviewed published and unpublished RCTs addressing the efficacy and safety of bleach baths for AD.

Methods

We completed this systematic review and meta-analysis according to Cochrane[18] and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidance[19] and report it according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] This review was prospectively registered (PROSPERO identifier: CRD4202123848).

Search Strategy and Selection Criteria

We searched MEDLINE, EMBASE, CENTRAL, and the World Health Organization International Clinical Trials Registry Platform for RCTs in any language comparing bleach baths to no bleach baths for patients with AD (see eAppendix 1 for the full search strategy). Forward and backward citation analysis of all included studies in our analysis and related systematic reviews listed in the Global Resource for Eczema Trials database using all Web of Science databases, including clinical experts on the guideline panel, identified additional potentially relevant studies. We contacted authors to obtain unpublished, missing, or clarification of data.

Calibrated paired reviewers independently screened records for titles and abstracts, followed by full texts, in duplicate for eligibility. We resolved discrepancies by consensus.

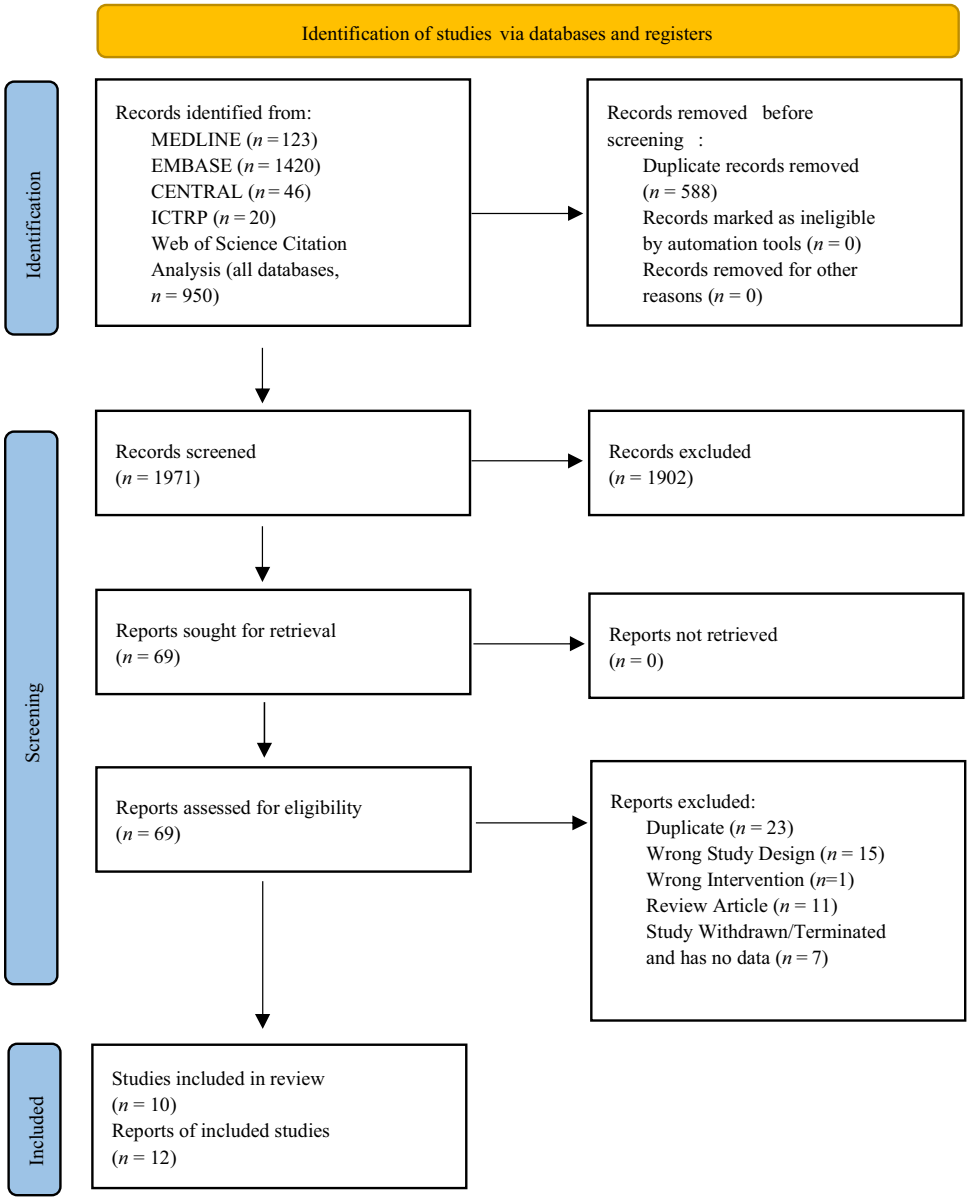


Figure 1. Study selection flowchart

Outcomes and Data Collection

Paired investigators independently extracted data in duplicate using a standardized, pilot-tested data extraction form on Microsoft Excel. We collected information on study characteristics, baseline demographics, control and intervention details, and outcome data. For data present only in graph form, we extracted values using WebPlotDigitizer 4.4 software.[21] We solved discrepancies by consensus.

Outcomes of interest were determined by a multidisciplinary collaborative panel consisting of patient and family partners with AD, clinicians (allergists, dermatologists, pediatricians, family medicine physicians, psychologists, nurse practitioners, pharmacists), and methodologists and aligned with the Harmonizing Outcome Measures for Eczema initiative.[22,23] The panel deemed critical outcomes for decision-making about bleach baths to include the following: clinician-reported severity; patient-reported severity (ie, extent of AD activity); patient-reported itch; adverse events of intervention; long-term control; flare (ie, event of AD activity requiring escalation of treatment); and infection. The panel further defined effects by ratio of means (RoMs) as trivial (RoM > 0.8), small (RoM < 0.8), moderate (RoM < 0.6), and large (RoM < 0.3).

Risk of Bias Assessment

We used the Cochrane Risk of Bias assessment tool to assess risk of bias on a per outcome basis for each study independently and in duplicate. Two reviewers each assigned the risk of bias as “low,” “some concerns,” or “high” for the following 6 domains: randomization process; deviation from intended outcome; missing outcome data; selection of reported results; measurement of outcome; and other bias.[24] We dichotomized “some concern” categories as probably low or probably high. Overall bias judgment rated studies as high risk of bias overall if 1 or more domain ratings were probably high risk of bias or high risk of bias and low risk of bias overall if all domain

Table 1
Characteristics of Included Studies

Author, year	Country	Follow-up (mo)	*n*	Age, mean (SD)	Male *n* (%)	Intervention	Comparator	Severity strata based on original scale[30]	Baseline clinician-reported severity, EASI mean (SD)[a]
Gonzalez et al,[41] 2016	United States	1	21	1.14 (1.41)	13 (61.9)	0.005% bleach, biw	Water bath	Moderate-severe	21.0 (10.65)
ACTRN12611000260921	New Zealand	1.5	16	5.1 (4.13)	10 (62.5)	0.0042% bleach, 5 min, biw	Water bath	Mild-severe	29.0 (10.74)
Hon et al,[42] 2016	People's Republic of China	1	40	12.1 (4.2)	23 (57.5)	0.005% bleach, 10 min, tiw	Water bath	Moderate -severe	38.2 (9.68)
Huang et al,[38] 2009	United States	3	31	7.1 (4.75)	15 (48.4)	0.005% bleach, 5-10 min, biw, mupirocin ung intranasal bid 5 consecutive d/mo, cephalexin 50 mg/kg/d tid initial 10 d	Water bath, petrolatum intranasal, cephalexin 50 mg/kg/d tid initial 10 d	Moderate-severe, with clinical infection at baseline	19.3 (11.76)
Khadka et al,[36] 2021	Mexico	3	28	11.04 (2.52)	11 (39.3)	0.006% bleach, biw, 10-15 min	Water bath	Moderate-severe	33.6 (11.27)
ACTRN12610000215022	Australia	1.5	41	4.3 (3.88)	23 (56.1)	0.005% bleach, tiw, cephalexin 15 mg/kg/d tid initial 10 d	Emollient baths (liquid paraffin 95% v/v) tiw, cephalexin 15 mg/kg/d tid initial 10 d	Moderate-severe	30.41 (6.22)
Shi et al,[40] 2016	United States	60 min	10	27.30 (11.51)	6 (60)	0.005% bleach, 10 min, once	Water bath	Mild-severe	27.08 (21.3)
NCT03619161	United States	1	58	7.19 (5.33)	28 (48.3)	0.005% bleach, 5-10 min, biw	Water bath ± bathroom cleaning with bleach	Mild-moderate	11.84 (8.74)
Wong et al[43], 2013	Malaysia	2	36	11.8 (6.92)	13 (30.95)	0.005% bleach, 10 min, biw, rinse with water, aqueous cream	Water bath	Moderate-severe	37.7 (13.69)

Abbreviations: bid, twice a day; biw, twice a week; EASI, Eczema Area Severity Index; tid, 3 times a day; tiw, 3 times a week; ung, ointment; v/v, volume (of solute) per volume (of solvent).
[a]Estimated values for scales other than EASI as detailed in the Methods section.

ratings were probably low risk of bias or low risk of bias. We used additional tools to assess risk of bias tailored to cluster-randomized, parallel-group trials, randomized crossover trials, and randomized parallel-group trials.[18]

Analysis

We analyzed all outcomes on an intention-to-treat basis, that is, all patients according to their assigned randomized arms. Frequentist DerSimonian and Laird and Frequentist and Bayesian generic inverse variance random-effects models generated pooled results to account for correlated data structures (eg, crossover or split-body study designs).

We summarized dichotomous outcomes using risk ratio (RR) and corresponding 95% credible interval (CrI) or confidence interval (CI). We combined continuous outcomes across studies using the mean difference (MD) and RoM. In case of studies reporting the same construct with different scales, we analyzed after conversion using linear transformation to a common scale and did sensitivity analyses according to standardized mean difference (SMD). To facilitate interpretability, we dichotomized clinician-reported severity into probability to improve by a 50% reduction and analyzed *S aureus* colonization as either growth or no growth when reported as a continuous measure.

We used GRADE to assess the certainty of the evidence[19,25,26] based on assessment of risk of bias, heterogeneity, imprecision, inconsistency, and publication bias, and used Making GRADE the Irresistible Choice application[27] to present the summary of findings table following standardized GRADE terminology.[28-30]

Prespecified sensitivity analyses to test the robustness of the findings included different time points across studies reporting clinician-reported severity, lesion-based *S. aureus* colonization, and varying severity of adverse events, and for additional analyses, using SMD and MD measurements, or different scales used to measure clinician-reported severity. In cases where SD values required estimation, we used a correlation coefficient of 0.7 and sensitivity analyses using the more conservative coefficient of 0.5.

We considered credibility of subgroup analyses using the following 8-core assessments from the Instrument to assess the Credibility of Effect Modification Analyses[31]: comparison of modifier based on between or within trials; similarity of results within trials; number of trials; consistency of observed effect direction with hypothesized direction a priori; credibility of interaction test (ie., *P* value); number of effect modifiers tested; use of random-effects model; and determination of cut points for continuous variables. Overall credibility judgment rated effect modifiers as very low credibility overall if all responses definitely or probably decrease credibility and high credibility overall if no responses definitely or probably decrease credibility. We used previously defined severity strata[32] to define the AD severity of the populations in the included studies.

We accounted for paired outcomes in crossover trials or split-body studies in a sensitivity analysis by using paired *t* tests for continuous outcomes. We analyzed individual patient data using analysis of covariance adjusting for baseline values and including a treatment by baseline interaction term for continuous outcomes and χ^2 tests for proportions. We accounted for missing data using multiple imputation with chained equations where applicable.

We performed analyses using Stata (versions 14.2 and 16; StataCorp, College Station, Texas) and RevMan (version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark). For Bayesian analyses, we used established informative priors for between-study heterogeneity,[33-35] hybrid Metropolis-Hastings sampling with blocked parameters, a 10,000-sample burn-in, 40,000 Markov Chain Monte Carlo (MCMC) samples, and confirmed convergence visually using overlain trace and density plots. We report associated posterior mean effects and 95% CrIs.

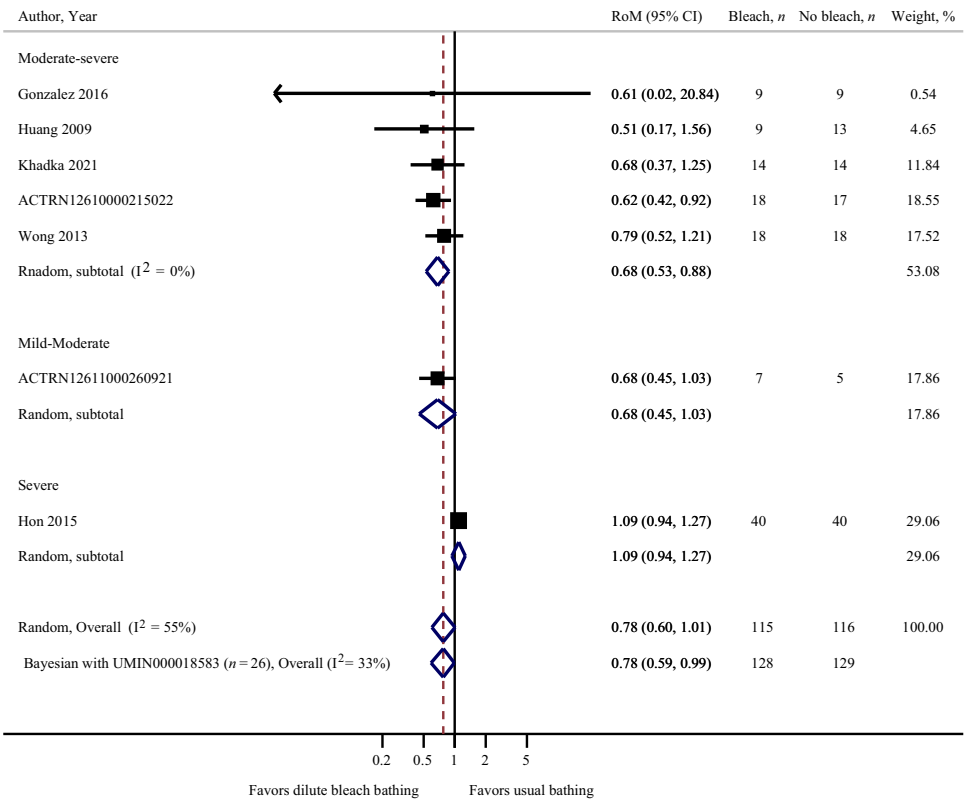


Figure 2. Forest plot showing estimates for the association of bleach baths with clinician-reported severity. CI, confidence interval; RoM, ratio of means.CI = confidence interval. RoM = ratio of means.

Results

We screened 2559 records and ultimately included 12 reports representing 10 RCTs, 4 unpublished (NCT03619161, ACTRN12610000215022, ACTRN12611000260921, and UMIN000018583) and 6 published[36-43] (Fig 1). We received individual patient data from 3 trials (ACTRN12610000215022 and NCT03619161).[36] One group did not share data on their 26-patient RCT (UMIN000018583); however, their stated qualitative findings suggested some difference in severity favoring bleach interventions (eAppendix 2). Correspondence with other authors revealed that they terminated all other trials registered globally (NCT03775590, NCT02582788, NCT01631617, NCT01286220, NCT04001855, NCT01826630, NCT02241174). The most commonly cited reason was disruption owing to the coronavirus disease 2019 (COVID-19) pandemic precluding any data collection, and therefore, 0 enrolled patients (eAppendix 2).

Table 1 summarizes the characteristics of the included studies (see eTable 1 for each study's detailed inclusion and exclusion criteria). The included studies enrolled 307 patients with mild-to-severe baseline AD severity (Scoring Atopic Dermatitis baseline mean of means 44.27 [median SD across trials, 13.21]); Eczema Area Severity Index (EASI) baseline mean of means 23.38 (median SD across trials, 11.76); median patients 28, interquartile (IQR) range 14-41; median of mean age 7.2 years (IQR, 4.7-12.0); 50.5% women; and a median follow-up of 6 weeks (IQR, 4-10). Estimated AD severity across all studies on a common scale (EASI) was mean of means 27.57 (median SD across trials, 10.74). Furthermore, 2 studies, 1 published[37,38] and 1 unpublished (NCT03619161), reported a history of bacterial infection.

Table 2
Anticipated Absolute Effects of Bleach Baths vs No Bleach Baths for Atopic Dermatitis Clinician-Reported Severity (EASI)

EASI categories	EASI score, no bleach	Difference with bleach baths vs no bleach baths		
		Mean	Lower 95% CrI	Upper 95% CrI
Mild	1	−0.2	−0.4	−0.01
Mild-moderate	10	−2.2	−4.1	−0.1
Moderate	20	−4.4	−8.2	−0.2
Moderate-severe	30	−6.6	−12.3	−0.3
Severe	40	−8.8	−16.4	−0.4
Severe	50	−11.0	−20.5	−0.5
Severe	60	−13.2	−24.6	−0.6
Severe	70	−15.4	−28.7	−0.7

Abbreviations: CrI, credible interval; EASI, Eczema Area Severity Index.

Risk of bias was mostly low or probably low across all outcomes (eAppendix 3). One study was at high risk of bias for early termination (ACTRN12611000260921) and one was probably high risk of bias owing to imbalance in baseline characteristics.[37,38] Risk of bias, however, did not modify overall pooled estimates. We did not identify strong evidence of publication bias (eFig. 2).No credible effect modifiers were identified for use of antibiotics at study start; age; publication status; different durations of intervention; frequency of bleach baths; regimented topical cortical steroid use; emollient use; type of comparator; history of bacterial infection; and risk of bias.

Outcomes

Atopic Dermatitis Severity

There were 8 studies that reported clinician-reported severity (n = 257) (ACTRN12611000260921, ACTRN12610000215022, UMIN000018583).[36-38,41-43] We harmonized all available data for this outcome with Bayesian approaches, including estimated data from the 26-patient RCT (UMIN000018583). Bleach baths probably improve AD severity compared with no bleach baths (RoM 0.78 [95% CrI, 0.59-0.99]; moderate certainty) (Fig 2). Effects were seen as soon as 4 weeks (eFig 3). Sensitivity analyses accounting for variation within studies were robust to findings (eTable 2). Anticipated

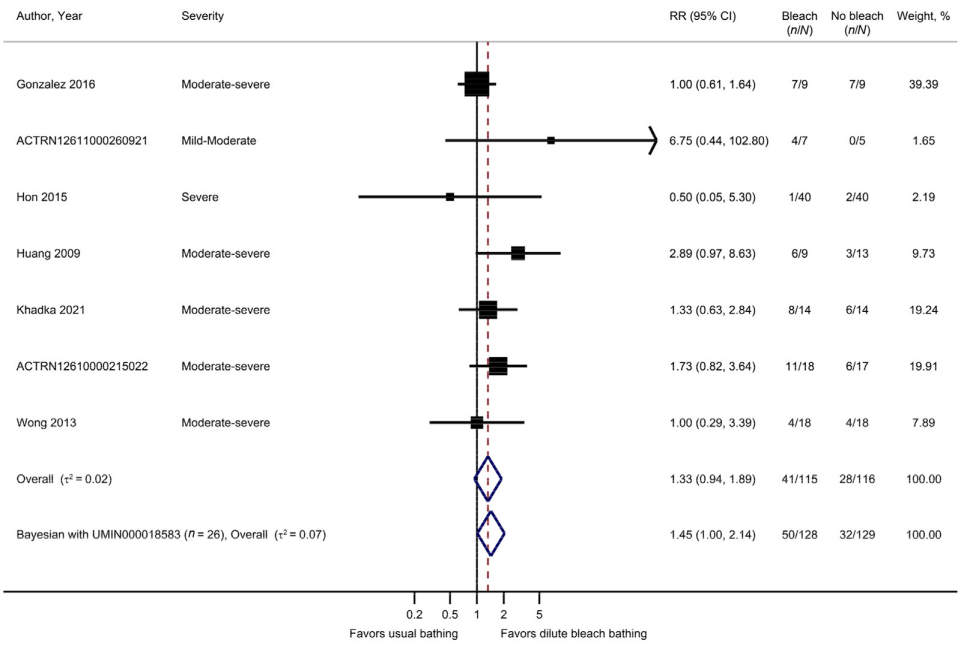


Figure 3. Probability (RR) to improve clinician-reported eczema severity by 50%. CI, confidence interval; RR, risk ratio.Note reversal of direction of x-axis. RR=relative risk.

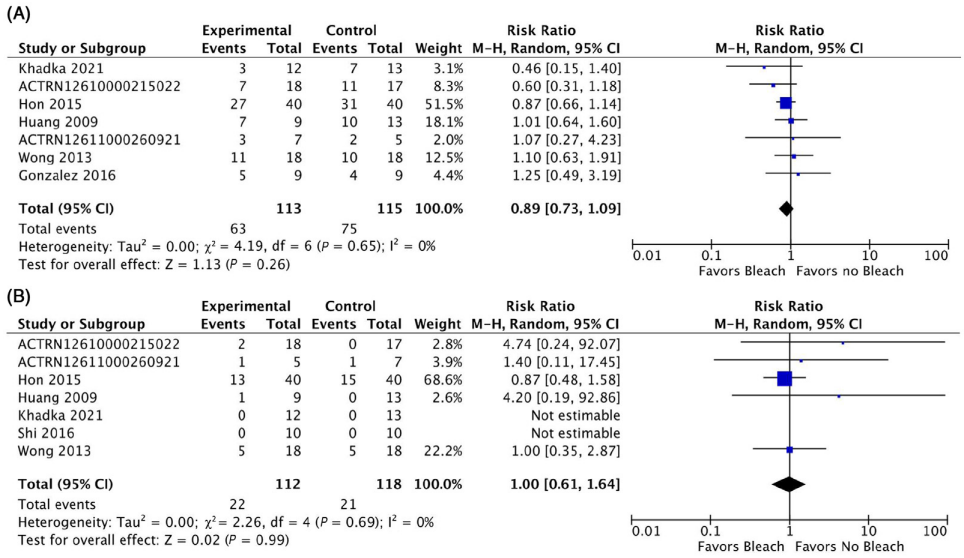


Figure 4. (A) *S aureus* colonization risk ratio; (B) Adverse events risk ratio. CI, confidence interval; M-H, Mantel-Haenszel.

Table 3
Bayesian Analysis of Eczema Severity (Incorporating the Patient Perspective or the skeptical and optimistic perspectives) by RoM

Prior	Plain language prior	Probability to improve eczema severity by at least a [x] . . .			
Type, N(mean, variance)	Text	Trivial effect(RoM > 0.8)	Small effect(RoM < 0.8)	Moderate effect(RoM < 0.6)	Large effect(RoM < 0.3)
Noninformative (weak pessimistic) (N [0,1])	Bleach baths have no effect and can worsen eczema	45.2	54.8	2.8	Highly improbable
Weak optimistic (N [-0.29,0.15])	Bleach baths slightly improve eczema	41.7	58.2	2.6	Highly improbable
Strong optimistic (N [-0.69,,0.35])	Bleach baths greatly improve eczema	36.8	63.2	4.5	Highly improbable

Abbreviation: RoM, ratio of means.

absolute effects of bleach baths vs no bleach baths for AD clinician-reported severity are in Table 2.

Across the included study populations, the pooled probability for AD severity to improve by 50% from baseline was 32% in the dilute bleach bathing group vs 22% in the control group (RR, 1.45 [95% CrI, 1.00-2.14]) (Fig 3).

S. aureus Colonization

There were 7 studies (n = 228) that reported how bleach baths affected *S. aureus* colonization (ACTRN12611000260921, ACTRN12610000215022).[36-38,41-43] Bleach may slightly decrease the chance of having a positive result of *S. aureus* skin culture (RR, 0.89 [95% CI, 0.73-1.09]; RD, −0.09 [−0.21 to 0.03], low certainty) (Fig 4A).

Adverse Events

There were 7 studies (n = 234) that reported adverse events (ACTRN12611000260921, ACTRN12610000215022).[36-40,42,43] Bleach-based interventions seem to cause little or no adverse effects (RR, 0.98 [95% CI, 0.60-1.61]; RD, 0.03 [95% CI, −0.05 to 0.10]) (Fig 4B). Most reported adverse events were mild and consisted of dry skin and irritation (xerosis and irritation, n = 5; dryness, n = 10; itch, n = 9; burning, n = 11). Furthermore, 3 studies (ACTRN12611000260921)[37,38,42] reported hospitalization with a total of 3 events (bleach, n = 1; control, n = 2). The hospitalization event in the bleach intervention was associated with incompliance and the development of a skin infection.[28,29]

Additional Outcomes

Additional outcomes included patient-reported itch, sleep quality, patient-reported AD severity, AD flare, and quality of life (eFig 3). There were 3 studies[36,42,43] (n = 144) that showed bleach baths may not improve patient-reported itch (pruritus visual analog scale [VAS]: 0-10, lower better; MD, −0.39 [95% CI, −1.85 to 1.08], low certainty). Furthermore, bleach baths may not improve sleep quality (2 studies,[36,42] n = 108, sleep scale 0-10, lower better; MD, −0.37 [95% CI, −1.51 to 0.76], low certainty). In addition, there were 2 studies (NCT03619161)[43] (n = 89) that reported patient-reported severity (Patient-Oriented Eczema Measure [POEM] MD, 0.99 [95% CI, −6.16 to 8.15], low certainty). The outcomes flare (NCT03619161) and quality of life[42] were reported in a single study each and were extremely imprecise (flare: n = 55; RR, 0.63 [95% CI, 0.07-5.67], very low certainty; quality of life—Children's Dermatology Life Quality Index [CDLQI]: n = 40; MD, −1.60 [−4.21 to 1.01], low certainty). No study reported data on long-term control (eg, RECAP) or occurrences of infection. Outcome scales are summarized in eTable 2.

Additional Analyses

Subgroup analysis for clinician-reported severity and the RoM showed no interaction by antibiotics at study start, age, publication status, different durations of intervention, analysis methods, or risk of bias (eTable 3). Credibility of subgroup analyses using the ICEMAN reveals very low to low credibility for all potential effect modifiers.

To facilitate interpretability, and to incorporate pessimistic and optimistic views regarding the efficacy of bleach baths, we did sensitivity analyses using a Bayesian framework (Table 3). Bayesian inference differs from frequentist statistics by accounting for uncertainty and quantifying the plausibility that any outcome effect is true rather than focusing on hypothesis testing.[44]

A summary of all findings is shown in Table 4.

Discussion

This systematic review and meta-analysis of 307 patients with moderate-to-severe AD in all available published and unpublished trials provides moderate-quality evidence that dilute bleach baths reduce clinician-reported AD severity by a relative 22% (MD in EASI of −6.06 for a baseline score of 27.57; 10 per 100 patients will improve severity by 50%) and cause little to no difference in adverse events. Many trials focused on surrogate microbiological outcomes rather than patient-relevant ones, such as patient-reported severity, patient-reported itch, long-term control, sleep quality, quality of life, and escalation of treatment.

Our findings are consistent with mechanistic data showing that bleach baths exert beneficial anti-inflammatory effects.[14] The relation between this and the microbiome, however, is less clear. We found low certainty evidence that bleach baths led to little to no difference in *S. aureus* burden, and similar effects of bleach baths in RCTs that co-administered antibiotics with bleach baths vs those that did not. Furthermore, the effects of bleach baths on *S. aureus* burden were inconsistent, transient, and did not clearly correlate with patient-important outcomes. Robust studies are required to better understand whether bleach baths function through their antimicrobial activity (including microbes other than *S. aureus*), direct-inflammatory activity, or some combination thereof. The skin microbiome profile of AD extends beyond *S. aureus* with influences of dysbiosis as an evolving topic of interest.[45,46]

The low certainty evidence for harms of bleach baths is in contrast to the higher certainty for its benefits. Patients self-administering bleach baths must carefully handle and dilute household cleaning solutions putting them at risk for injury and adverse effects.[47] One study[28,29] reported hospitalization associated with incompliance with bleach interventions. Narrative reviews and our guideline panel's clinical experience are also consistent with the potential for bleach bathing may sometimes result in improper administration and adverse events.[47] Robust RCTs are clearly required to improve the evidence for safety of bleach baths for AD.

The clinical and research implications of our findings showing a probable modest effect in improving 1 of 8 prespecified patient-important outcomes suggests at least 3 things. First, recommendations for bleach baths to treat AD should carefully consider the wide availability and low cost of bleach against the residual uncertainty in other outcomes, albeit clinical opinion suggests that it is generally safe, and in context of patient values and preferences. Second, the relative decrease of 22% in AD severity provides patient-important relief in those with high disease activity (eg, a patient with an EASI of 40 might improve by 8.8 points) and likely will be of trivial benefit in those presenting with low disease activity (eg, a patient with an EASI of 10 might improve by 2.2 points) (Table 2). Third, large definitive RCTs are required to fully inform the benefits and harms of bleach baths and to further understand and confirm the mechanism of bleach on AD. Termination of all other RCTs globally further underscores this (eAppendix 1). A target trial sample size depends on severity of AD. A target trial sample size calculation defined by a power of 0.95 and a significance level of 0.05 suggests that a 200-patient RCT with moderate-severe AD could prove definitive (eTable 4).

The strengths of our review include a comprehensive search strategy with no language restrictions, incorporation of previously unpublished data, Bayesian analyses, multistakeholder input, focus on patient-important effects, and conduct and interpretation according to Cochrane and GRADE standards. Compared with previous reviews,[13,16,17] we include more than double the number of RCTs and participants. We corresponded with authors globally and confirmed termination of all other RCTs around the world.

There are several limitations. One author did not share any precise quantitative data regarding their 26-patient RCT, though their description of their findings and our Bayesian analyses addressed

Table 4
Summary of Findings

Dilute bleach bathing compared with usual bathing for the treatment of atopic dermatitis (eczema)					
Outcome	Study results and measurements	Absolute effect estimates No bleach	Bleach	Certainty of the Evidence (Quality of evidence)	Plain language summary
Clinician-reported severity	**Ratio of means: 0.78** (95% CrI, 0.59-0.99) Measured by: Eczema area severity index Scale: 0-72, lower better **Risk ratio to improve by 50%: 1.45** (95% CrI, 1.00-2.14) Based on 257 patients in 8 RCTs (ACTRN12611000260921, ACTRN12610000215022, UMIN000018583)[35-37,40-42]	**27.57** Mean **22** per 100 improve by 50% Difference: **MD, 6.06 lower** (95% CrI, 11.30 lower-0.28 lower) **or 10 more per 100 improve** (95% CrI, 0-26 more)	**21.50** Mean **32** per 100 improve by 50%	**Moderate** Owing to serious imprecision[a]	Dilute bleach bathing probably improves clinician-reported severity. The absolute change in severity scores may depend on baseline severity before treatment.
S aureus colonization	**Risk ratio: 0.89** (95% CI, 0.73-1.09) Based on 228 patients in 7 RCTs (ACTRN12611000260921, ACTRN12610000215022)[35-37,40-42]	**65** per 100 Difference: **7 fewer per 100** (95% CI, 17 fewer-6 more)	**58** per 100	**Low** Owing to very serious imprecision[b]	Dilute bleach bathing may slightly decrease *S. aureus* colonization.
Adverse events - Any events	**Risk ratio: 0.98** (95% CI, 0.6-1.61) Based on 234 patients in 7 RCTs (ACTRN12611000260921, ACTRN12610000215022)[35-39,41,42,47]	**18** per 100 Difference: **1 fewer per 100** (95% CI, 7 fewer-11 more)	**17** per 100	**Low** Owing to very serious imprecision[b]	Dilute bleach bathing may have little or no difference on adverse events.
Patient-reported itch	Measured by: Visual analogue scale Scale: 0-10, lower better Based on 144 patients in 3 RCTs[35,41,42]	**5.78** Mean Difference: **MD 0.39 lower** (95% CI, 1.85 lower-1.08 higher)	**5.39** Mean	**Low** Owing to very serious imprecision[b]	Dilute bleach bathing may have little or no difference on patient-reported itch.
Patient-reported severity	Measured by: Patient-oriented eczema measure Scale: 0-28, lower better Based on 89 patients in 2 RCTs (NCT03619161)[42]	**15.40** Mean Difference: MD **0.99 higher** (6.16 lower to 8.15 higher)	**14.41** Mean	**Low** Owing to very serious imprecision[b]	Dilute bleach bathing may have little or no difference on patient-reported severity.
Sleep quality	Measured by: Measured by: Subjective SCORAD - Sleep Scale: 0-10, lower better Based on 108 patients in 2 RCTs[35, 41]	**3.95** Mean Difference: **MD 0.37 lower** (95% CI, 1.51 lower-0.76 higher)	**3.58** Mean	**Low** Owing to very serious imprecision[b]	Dilute bleach bathing may slightly improve sleep quality.
Flare	**Risk ratio: 0.63** (95% CI, 0.07-5.67) Based on 55 patients in 1 RCT (NCT03619161)	**8** per 100 Difference: **3 fewer per 100** (95% CI, 8 fewer-39 more)	**5** per 100	**Very low** Owing to extremely serious imprecision[c]	We are uncertain whether dilute bleach bathing increases or decreases flare.
Quality of life	Measured by: Children's dermatology life quality index Scale: 0-30, lower better Based on 80 patients in 1 RCT[41]	**10.07** Mean Difference: **MD 1.60 lower** (95% CI, 4.21 lower-1.01 higher)	**8.47** Mean	**Low** Owing to very serious imprecision[d]	Dilute bleach bathing may slightly improve AD-related quality of life.

Abbreviations: CI, confidence interval; CrI, credible interval; MD, mean difference; RCT, randomized controlled trial; *S aureus*, *Staphylococcus aureus*.
Values in bold according to GRADE format[25].
[a]Imprecision: serious. Small number of patients (n < 400).[26]
[b]Imprecision: very serious. Small number of patients (n < 400).
[c]Imprecision: extreme serious. Only data from one small study (n < 400); wide CIs (CI approaching 1).
[d]Imprecision: very serious. Only data from one small study n (< 400).

this. The included studies were heterogeneous and had typically small populations that powered their studies using surrogate outcomes as primary end points rather than patient-relevant ones, and 1 study was terminated early (ACTRN12611000260921). We addressed these using structured risk of bias appraisal and GRADE ratings and provide sample size estimates of what a definitive RCT might require. Few studies reported other patient-important outcomes, such as patient-reported severity, quality of life, and adverse effects, which we appraised using GRADE and acknowledge in the Summary of Findings (Table 4).

This review, synthesizing the totality of evidence to date and with no more trials registered, provides moderate-quality evidence that bleach baths 2 to 3 times per week probably improve AD severity by a modest amount and possibly promote little to no adverse events. These findings support patients, clinicians, researchers, and policymakers in striving for optimal outcomes for patients with AD.

References

1. Fishbein AB, Silverberg JI, Wilson EJ, Ong PY. Update on atopic dermatitis: diagnosis, severity assessment, and treatment selection. *J Allergy Clin Immunol Pract*. 2020;8(1):91–101.
2. Silverberg JI, Barbarot S, Gadkari A, Simpson EL, Weidinger ES, Mina-Osorio P, et al. Atopic dermatitis in the pediatric population: a cross-sectional, international epidemiologic study. *Ann Allergy Asthma Immunol*. 2021;126(4). 417-428.e2.
3. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy*. 2018;73(6):1284–1293.
4. Bridgman AC, Block JK, Drucker AM. The multidimensional burden of atopic dermatitis: an update. *Ann Allergy Asthma Immunol*. 2018;120(6):603–606.
5. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol*. 2009;124(6). 1251-1258.e23.
6. Mancuso JB, Lee SS, Paller AS, Ohya Y, Eichenfield LF. Management of severe atopic dermatitis in pediatric patients. *J Allergy Clin Immunol Pract*. 2021;9(4):1462–1471.
7. Barnes TM, Greive KA. Use of bleach baths for the treatment of infected atopic eczema. *Australas J Dermatol*. 2013;54(4):251–258.
8. Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol*. 2013;131(2). 295-299.e1-e27.
9. Peck B, Workeneh B, Kadikoy H, Patel S, Abdellatif A. Spectrum of sodium hypochlorite toxicity in man - also a concern for nephrologists. *NDT Plus*. 2011;4(4):231–235.
10. Gong JQ, Lin L, Lin T, Hao F, Zeng FQ, Bi ZG, et al. Skin colonization by Staphylococcus aureus in patients with eczema and atopic dermatitis and relevant combined topical therapy: a double-blind multicentre randomized controlled trial. *Br J Dermatol*. 2006;155(4):680–687.
11. Abeck D, Mempel M. Staphylococcus aureus colonization in atopic dermatitis and its therapeutic implications. *Br J Dermatol*. 1998;139(Suppl 53):13–16.
12. Ong PY. Recurrent MRSA skin infections in atopic dermatitis. *J Allergy Clin Immunol Pract*. 2014;2(4):396–399.
13. George SM, Karanovic S, Harrison DA, Rani A, Bimie AJ, Bath-Hextall FJ, et al. Interventions to reduce Staphylococcus aureus in the management of eczema. *Cochrane Database Syst Rev*. 2019;2019:(10) CD003871.
14. Sawada Y, Tong Y, Barangi M, Hata T, Williams MR, Nakatsuji T, et al. Dilute bleach baths used for treatment of atopic dermatitis are not antimicrobial in vitro. *J Allergy Clin Immunol*. 2019;143(5):1946–1948.
15. Leung TH, Zhang LF, Wang J, Ning S, Knox SJ, Kim SK. Topical hypochlorite ameliorates NF-κB-mediated skin diseases in mice. *J Clin Invest*. 2013;123(12):5361–5370.
16. Maarouf M, Shi VY. Bleach for atopic dermatitis. *Dermatitis*. 2018;29(3):120–126.
17. Chopra R, Vakharia PP, Sacotte R, Silverberg JI. Efficacy of bleach baths in reducing severity of atopic dermatitis: a systematic review and meta-analysis. *Ann Allergy Asthma Immunol*. 2017;119(5):435–440.
18. Higgins JP, Thomas J, Chandler J, et al. *Cochrane Handbook for Syst. Rev. of Interventions*. John Wiley & Sons; 2019.
19. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924–926.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group PRISMA. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLOS Med*. 2009;6:(7) e1000097.
21. Webplotdigitizer RA: Version 4.4; 2020. https://automeris.io/WebPlotDigitizer/.
22. Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin Immunol*. 2014;134(4):800–807.
23. Schmitt J, Langan S, Williams HC. European Dermato-Epidemiology Network. What are the best outcome measurements for atopic eczema? A systematic review. *J Allergy Clin Immunol*. 2007;120(6):1389–1398.
24. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
25. Chu DK, Golden DBK, Guyatt GH. Translating evidence to optimize patient care using GRADE. *J Allergy Clin Immunol Pract*. 2021;9(12):4221–4230.
26. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence-imprecision. *J Clin Epidemiol*. 2011;64(12):1283–1293.
27. *Making GRADE the Irresistible Choice*. https://magicevidence.org/magicapp/.
28. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol*. 2020;119:126–135.
29. Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. *J Clin Epidemiol*. 2013;66(2):173–183.
30. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383–394.
31. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ*. 2020;192(32):E901–E906.
32. Chopra R, Vakharia PP, Sacotte R, Patel N, Immaneni S, White T, et al. Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis. *Br J Dermatol*. 2017;177(5):1316–1321.
33. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol*. 2012;41(3):818–827.
34. Rhodes KM, Turner RM, Higgins JP. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. *J Clin Epidemiol*. 2015;68(1):52–60.
35. Rhodes KM, Turner RM, White IR, Jackson D, Spiegelhalter DJ, Higgins JP. Implementing informative priors for heterogeneity in meta-analysis using meta-regression and pseudo data. *Stat Med*. 2016;35(29):5495–5511.
36. Khadka VD, Key FM, Romo-González C, Martínez-Gayosso A, Campos-Cabrera BL, Gerónimo-Gallegos A, et al. The skin microbiome of patients with atopic dermatitis normalizes gradually during treatment. *Front Cell Infect Microbiol*. 2021;11:720674.
37. Huang JT, Rademaker A, Paller AS. Dilute bleach baths for Staphylococcus aureus colonization in atopic dermatitis to decrease disease severity. *Arch Dermatol*. 2011;147(2):246–247.
38. Huang JT, Abrams M, Tlougan B, Rademaker A, Paller AS. Treatment of Staphylococcus aureus colonization in atopic dermatitis decreases disease severity. *Pediatr*. 2009;123(5):e808–e814.
39. Shi V, Foolad N, Takeda N, et al. The effect of dilute bleach bath and moisturizers on skin barrier function in atopic dermatitis. *J Am Acad Dermatol*. 2015;72:AB76.
40. Shi V, Foolad N, Ornelas J, Hassoun LA, Monico G, Takeda N, et al. Comparing the effect of bleach and water baths on skin barrier function in atopic dermatitis: a split-body randomized controlled trial. *Br J Dermatol*. 2016;175(1):212–214.
41. Gonzalez ME, Schaffer JV, Orlow SJ, Gao Z, Li H, Alekseyenko AV, et al. Cutaneous microbiome effects of fluticasone propionate cream and adjunctive bleach baths in childhood atopic dermatitis. *J Am Acad Dermatol*. 2016;75(3). 481-493.e8.
42. Hon KL, Tsang YCK, Lee VWY, Pong NH, Ha G, Lee ST, et al. Efficacy of sodium hypochlorite (bleach) baths to reduce Staphylococcus aureus colonization in childhood onset moderate-to-severe eczema: a randomized, placebo-controlled cross-over trial. *J Dermatol Treat*. 2016;27(2):156–162.
43. Sm Wong, Ng TG, Baba R. Efficacy and safety of sodium hypochlorite (bleach) baths in patients with moderate to severe atopic dermatitis in Malaysia. *J Dermatol*. 2013;40(11):874–880.
44. Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR. Methods in health service research. An introduction to Bayesian methods in health technology assessment. *BMJ*. 1999;319(7208):508–512.
45. Bjerre RD, Bandier J, Skov L, Engstrand L, Johansen JD. The role of the skin microbiome in atopic dermatitis: a systematic review. *Br J Dermatol*. 2017;177(5):1272–1278.
46. Nakatsuji T, Gallo RL. The role of the skin microbiome in atopic dermatitis. *Ann Allergy Asthma. Immunol.*. 2019;122(3):263–269.
47. Collier E, Sangar S, Shen A, Davis J. A closer look at bleach baths: evidence, tub size, and instructions [e-pub ahead of print]. *Dermatology*. doi:10.1159/000518770, accessed November 25, 2021.

eAppendix 1. **Search Strategy**

EMBASE

1. exp hypochlorite/
2. exp hypochlorite sodium/ or exp bleaching agent/
3. hypochlorite.mp.
4. hypochlorite sodium.mp.
5. bleach.mp.
6. 1 or 2 or 3 or 4 or 5
7. eczema.mp. or exp eczema/
8. dermatitis.mp. or exp atopic dermatitis/ or exp dermatitis/
9. neurodermatitis.mp. or exp neurodermatitis/
10. Besnier$ Prurigo.mp.
11. 7 or 8 or 9 or 10
12. 6 and 11

MEDLINE

1. exp Eczema/ or eczema.mp.
2. exp Dermatitis/ or exp Dermatitis, Atopic/ or dermatitis.mp.
3. neurodermatitis.mp. or exp Neurodermatitis/
4. Besnier$ Prurigo.mp.
5. 1 or 2 or 3 or 4
6. Sodium Hypochlorite/
7. hypochlorite.mp. or exp Hypochlorous Acid/
8. bleach.mp.
9. Sodium Hypochlorite.mp.
10. 6 or 7 or 8 or 9
11. 5 and 10

CENTRAL

1. MeSH descriptor: [Eczema] explode all trees
2. MeSH descriptor: [Dermatitis, Atopic] explode all trees
3. MeSH descriptor: [Neurodermatitis] explode all trees
4. MeSH descriptor: [Dermatitis] explode all trees
5. eczema or dermatitis or neurodermatitis:ti,ab,kw
6. besnier$ prurigo:ti,ab,kw
7. {or #1-#6}
8. MeSH descriptor: [Sodium Hypochlorite] explode all trees
9. MeSH descriptor: [Hypochlorous Acid] explode all trees
10. sodium hypochlorite or hypochlorite or hypochlorous acid or bleach:ti,ab,kw
11. {or #8-#10}
12. #7 and #11

ICTRP

- Bleach or Hypochlorite

eAppendix 2. **Correspondence With Authors**

Study ID	Information received
NCT03775590	Date: January 26, 2021 Contact: Megha Tollefson Emailed response: Study is withdrawn/terminated and has no data Reason for termination: Difficulty enrolling patients and COVID-19 pandemic
NCT01631617	Date: February 23, 2021 Contact: Heidi Kong Emailed response: Study is withdrawn/terminated and has no data Reason for termination: Difficulty enrolling patients
NCT02241174	Date: February 23, 2021 Contact: Jamaine Cruz Study status: Withdrawn/terminated and has no data
NCT01826630	Date: February 23, 2021 Contact: Matthew Zirwas Emailed response: Study is withdrawn/terminated and has no data
NCT02582788	Date: February 23, 2021 Contact: Megha Tollefson Study status: Withdrawn/terminated and has no data
NCT01286220	Date: March 4, 2021 Contact: Amit Pandya Emailed response: Study is withdrawn/terminated and has no data Reason for termination: Logistical errors
UMIN000018583	Date: April 13, 2021 Contact: Hiroshi Kawasaki Emailed response: qualitative data shared "We performed a clinical study on bleach bath therapy in 26 patients with atopic dermatitis. What we learned from this study is that there are differences in therapeutic effects depending on the case. Although the number of cases is small and there are some differences in severity, we think that about 70% of the patients showed a good effect. Currently, we are analyzing whether this difference in therapeutic effect is related to the difference in skin microbiome, and we plan to publish the results after this analysis."
NCT04001855	Date: June 15, 2021 Contact: Vivian Shi Emailed response: Portion of raw data set was lost and they will no longer seek publication; no data shared.

eAppendix 3. **Cochrane Risk of Bias**

Study (Parallel)	Randomization	Deviations from intended intervention *	Missing outcome data	Measurement of outcome	Selection of reported results	Other Bias	Overall
Gonzalez 2016							
ACTRN12611000260921 †							
Huang 2009 ‡							
Khadka 2021							
ACTRN12610000215022							
NCT03619161							
Wong 2013							

Study (Cross-over)	Randomization	Carryover effects	Deviations from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported results	Other Bias	Overall
Hon 2015								

Study (Split-body)	Randomization	Patient recruitment	Deviations from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported results	Other Bias	Overall
Shi 2016								

† Probably high risk of bias for early termination
‡ Probably high risk of bias due to imbalance in baseline characteristics

[a]Some studies suggested it may be difficult to blind participants to intervention owing to the potential smell of dilute bleach. Deviations from the intended intervention, however, would be unlikely, and if present would have led to smaller estimated effects than those found, and regardless, outcome assessors were blinded to clinician-adjudicated outcomes (eg, EASI).

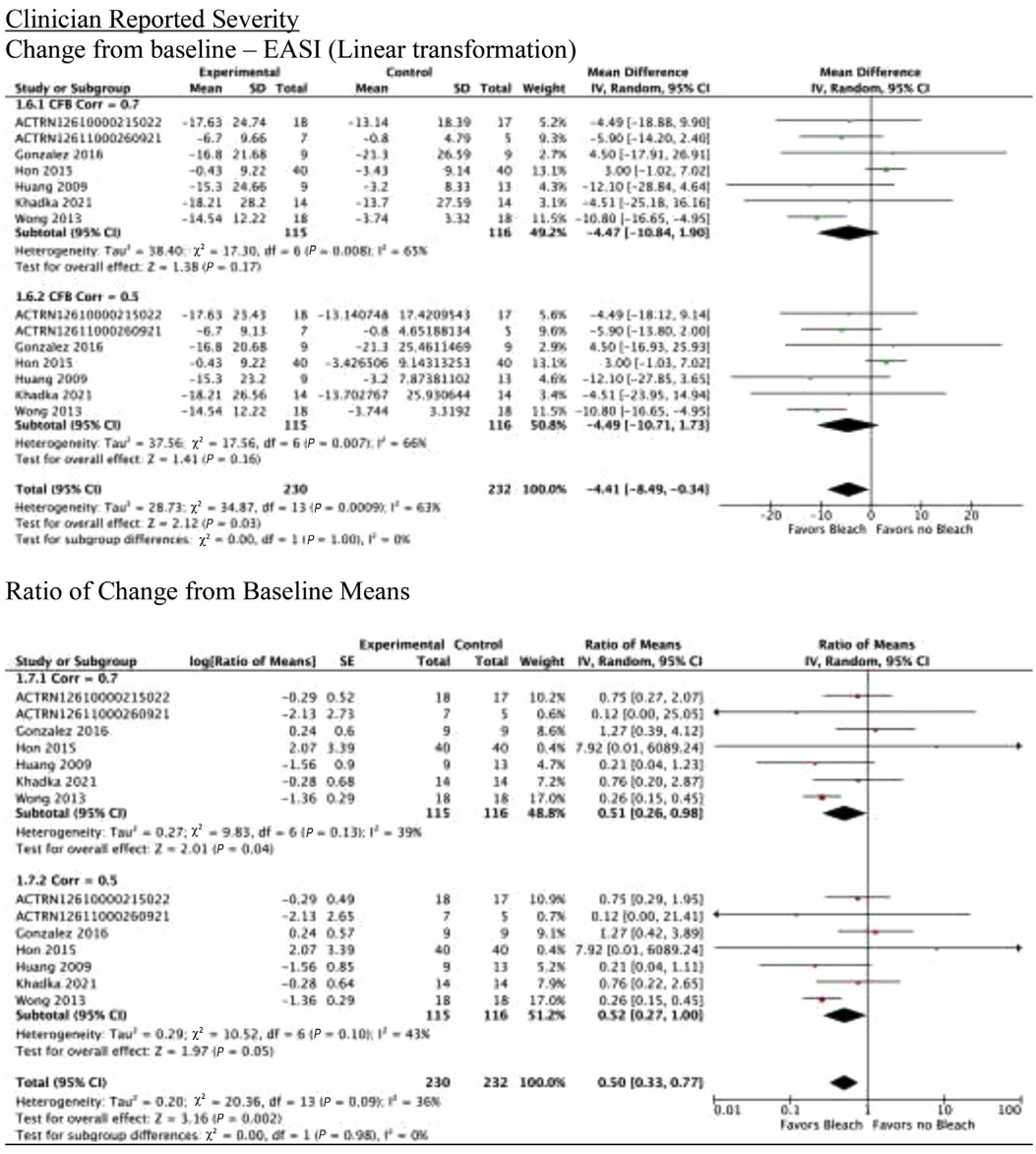
[b]Probably high risk of bias for early termination.

[c]Probably high risk of bias owing to imbalance in baseline characteristics.

eTable 1
Inclusion and Exclusion Criteria

Study	Inclusion Criteria	Exclusion Criteria
Gonzalez et al,[41] 2016	3 mo to 5 yo, moderate-to-severe AD	Patients with concurrent chronic inflammatory skin disorders or using/had used systemic or topical antibiotics for AD in the prior 2 wk
ACTRN12611000260921	1-15 yo with AD	Antibiotics within 6 wk before enrolment or history of adverse reactions to bleach
Hon et al,[42] 2016	4-18 yo, moderate-severe SCORAD (>15), teaching hospital clinic, with *S aureus* colonization (skin swab cultures)	Oral antibiotics in past 4 wk, intercurrent illness for 2 wk before study, and coexisting skin diseases other than eczema
Huang et al,[38] 2009	6 mo to 17 yo, moderate-severe AD (per IGA), signs of skin infection (weeping, crusting, or pustules)	Current or recent use (within the past 8 wk) of topical or oral antibiotic preparations and allergy to cephalosporins or mupirocin
Khadka et al,[36] 2021	5-18 yo, moderate-to-severe SCORAD 25+	No topical or systemic antibiotics in past month
ACTRN12610000215022	6 mo to 18 yo, SCORAD 25+	Known sensitivity to bleach; had treatment with diluted bleach baths, antiseptic bath oils, diluted salt baths; or antibiotics therapy within 4 wk before randomization and has clinical signs of a current viral skin infection
Shi et al,[40] 2016	8-65 yo, diagnosed with AD by a board-certified dermatologist at UC Davis	Those who are pregnant, prisoners, or cognitively impaired
NCT03619161	6 mo to 17 yo, moderate-severe AD (10% BSA, on a class 1 topical steroid or systemic immunosuppressive agent)	Patient or family member having a sensitivity to bleach or patient having used bleach baths within the previous 2 mo
Wong et al,[43] 2013	2-30 yo, moderate-severe AD (per Rajka and Langeland 1989)	Known sensitivity to bleach, had eczema herpeticum or other cutaneous infections, patients who were on systemic antibiotics or systemic corticosteroids at the time of recruitment or during the study period, those on other antiseptic baths, and patients who were pregnant or lactating

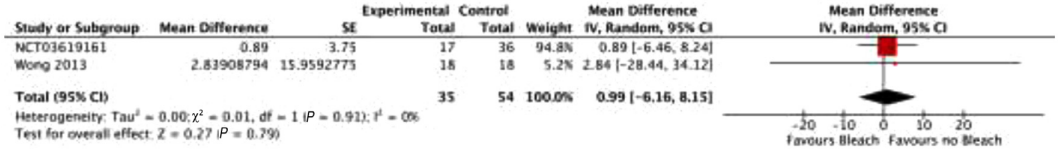
Abbreviations: AD, atopic dermatitis; BSA, body surface area; IGA, Investigator Global Assessment; mo, month old; SCORAD, Scoring Atopic Dermatitis; yo, year old.



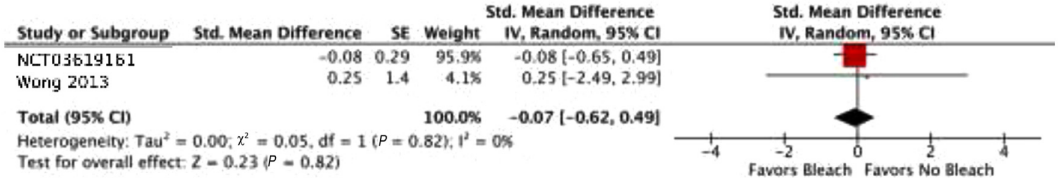
eFigure 1. Funnel plots. MD, mean difference; RD, risk difference; RR, risk ratio.

Patient reported severity

Mean Difference – Linear Transformation POEM

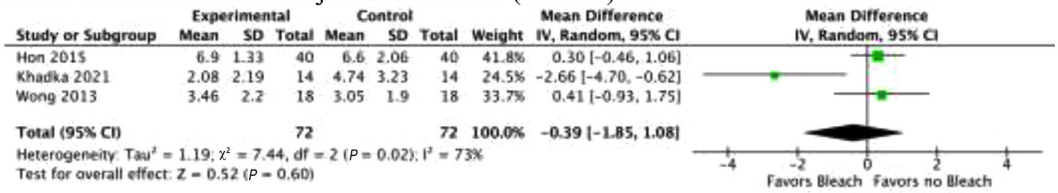


Standard Mean Difference

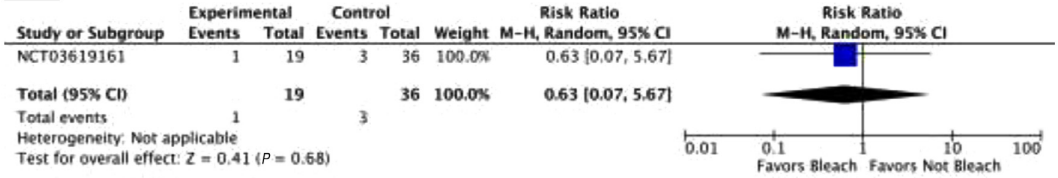


Patient reported itch

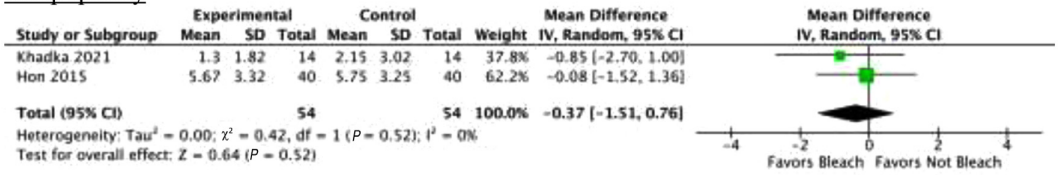
Linear Transformation – Subjective SCORAD (Pruritus)



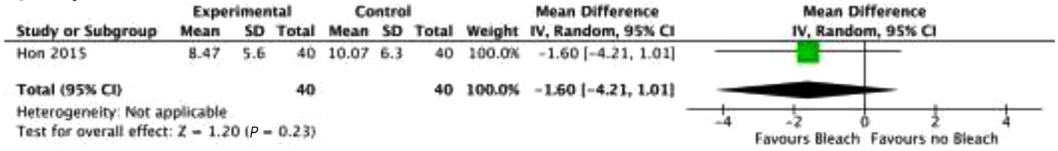
Flare



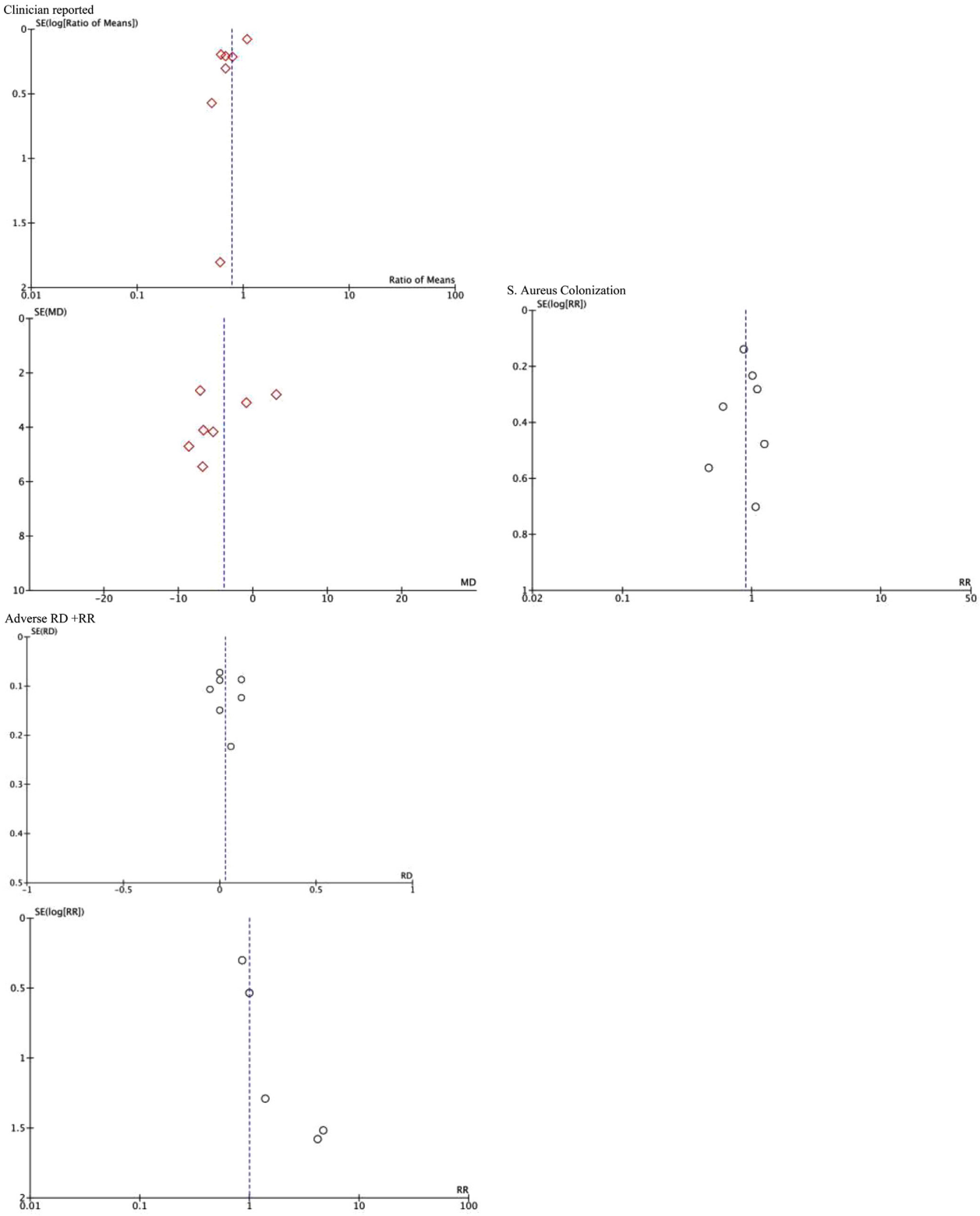
Sleep quality



Quality of life



eFigure 1 Continued.

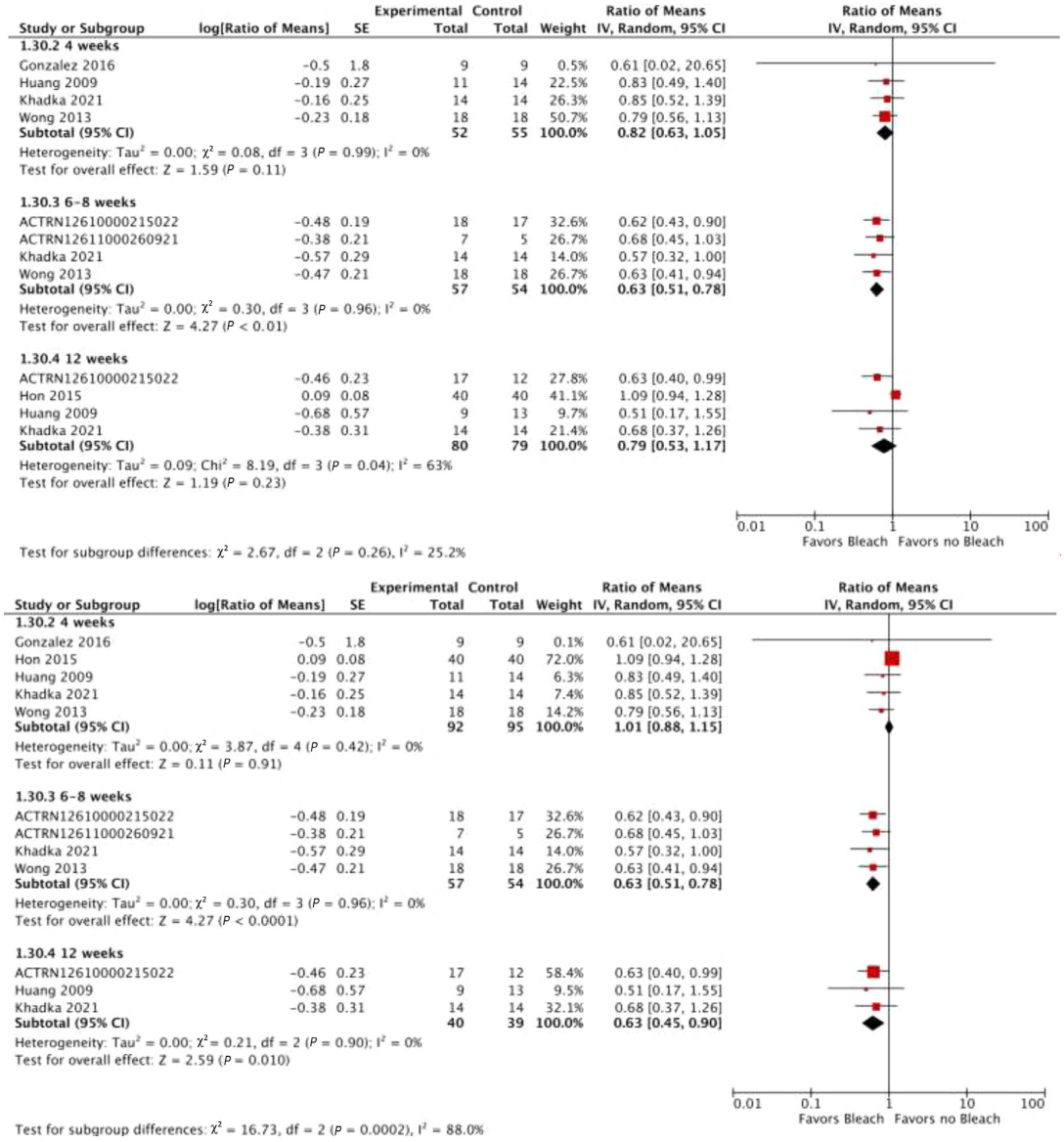


eFigure 2. Bleach interventions at different time points. CI, confidence interval.

eTable 2
Sensitivity Analyses

Characteristic	Clinician-reported severity—SMD (Hedges' g)	Clinician-reported severity—RoM
Varying outcome scales		
SCORAD	SMD, −0.39 (95% CI, −0.77 to −0.00)	RoM, 0.78 (95% CI, 0.61-1.01)
EASI	SMD, −0.37 (95% CI, −0.75 to 0.00)	RoM, 0.77 (95% CI, 0.59-1.02)
IGA	SMD, −0.42 (95% CI, −0.81 to −0.04)	RoM, 0.77 (95% CI, 0.60-1.00)
BSA	SMD, −0.44 (95% CI, −0.86 to −0.03)	RoM, 0.73 (95% CI, 0.55-0.98)
Change from baseline—linear transformation		
CORR = 0.5	SCORAD MD, −6.43 (95% CI, −15.33 to 2.47) EASI MD, −4.49 (95% CI, −10.72 to 1.73)	N/A
CORR = 0.7	SCORAD MD, −6.40 (95% CI, −15.50 to 2.71) EASI MD, −4.47 (95% CI, −10.83 to 1.89)	N/A
Change from baseline (SMD and ratio of changes from baseline)		
CORR = 0.5	SMD, −0.31 (95% CI, −0.76 to 0.14)	RoM, 0.51 (95% CI, 0.27-0.99)
CORR = 0.7	SMD, −0.30 (95% CI, −0.74 to 0.15)	RoM, 0.51 (95% CI, 0.26-0.98)
Time point of intervention		
First follow-up	SMD, −0.30 (95% CI, −0.66 to 0.05)	RoM, 0.83 (95% CI, 0.67-1.02)
Previous follow-up	SMD, −0.39 (95% CI, −0.77 to −0.01)	RoM, 0.78 (95% CI, 0.61-1.01)
Variations within studies		
Khadka—no multiple imputation	SMD, −0.38 (95% CI, −0.77 to 0.00)	RoM, 0.79 (95% CI, 0.61-1.02)
Hon—unpaired *t* test (n = 20)	SMD, −0.41 (95% CI, −0.75 to −0.07)	RoM, 0.78 (95% CI, 0.62-0.99)
S aureus colonization		
Greatest *S aureus* colonization	RR, 0.89 (95% CI, 0.73-1.09)	
Lesional *S aureus* colonization	RR, 0.87 (95% CI, 0.63-1.19)	
Adverse events	Risk ratio	Risk difference
Sensitivity analysis		
Varying severity		
Any AE	0.98 (95% CI, 0.60-1.61)	0.04 (95% CI, −0.05 to 0.10)
Mild AE	1.29 (95% CI, 0.68-2.46)	0.04 (95% CI, −0.03 to 0.11)
AE leading to hospitalization	0.78 (95% CI, 0.13-4.71)	−0.01 (95% CI, −0.06 to 0.03)

Abbreviations: AE, adverse event; BSA, body surface area; CI, confidence interval; EASI, Eczema Area Severity Index; IGA, Investigator Global Assessment; MD, mean difference, N/A, not applicable; RoM, ratio of means; RR, risk ratio; SCORAD, Scoring Atopic Dermatitis; SMD, Standardized Mean Difference.



eFigure 3. Additional outcomes. CI, confidence interval; EASI, Eczema Area Severity Index; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis.

eTable 3
Outcome Scale

Measure	Range of scale	Direction of scale
Clinician-reported severity		
SCORAD	0-103	Lower better
EASI	0-72	Lower better
IGA	0-4	Lower better
BSA	0-100	Lower better
Patient-reported itch		
VAS	1-10	Lower better
Subjective SCORAD—itch	0-10	Lower better
Patient-reported severity		
POEM	0-28	Lower better
Quality of life		
CDLQI	0-30	Lower better

Abbreviations: BSA, body surface area; CDLQI, children dermatology life quality index; EASI, Eczema Area Severity Index; IGA, Investigator Global Assessment; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; VAS, visual analog scale.

eTable 4
Subgroup Analyses

Subgroups Subgroup analysis	Clinician-reported severity	*S aureus* colonization	Adverse events
Use of Abx at study start			
Without Abx	RoM, 0.86 (95% CI, 0.66-1.11)	RR, 0.91 (95% CI, 0.72-1.14)	RR, 0.90 (95% CI, 0.54-1.50)
With Abx	RoM, 0.61 (95% CI, 0.42-0.88)	RR, 0.45 (95% CI, 0.04-4.48)	RR, 4.47 (95% CI, 0.52-38.09)
$P_{interaction}$	.14	.55	.15
Credibility	Very low	Very low	Very low
Age			
Pediatric	RoM, 0.76 (95% CI, 0.55-1.05)	RR, 0.80 (95% CI, 0.54-1.20)	RR, 0.98 (95% CI, 0.56-1.72)
Pediatric and adult	RoM, 0.79 (95% CI, 0.52-1.21)	RR, 1.10 (95% CI, 0.63-1.91)	RR, 1.00 (95% CI, 0.35-2.87)
$P_{interaction}$	.88	.37	.97
Credibility	Very low	Very low	Very low
Publication status			
Published	RoM, 0.91 (95% CI, 0.71-1.17)	RR, 0.92 (95% CI, 0.75-1.13)	RR, 0.94 (95% CI, 0.56-1.57)
Unpublished	RoM, 0.65 (95% CI, 0.49-0.86)	RR, 0.43 (95% CI, 0.07-2.76)	RR, 1.96 (95% CI, 0.28-13.82)
$P_{interaction}$	.08	.42	.47
Credibility	Low	Very low	Very low
RoB			
Low RoB	RoM, 0.82 (95% CI, 0.61-1.11)	RR, 0.78 (95% CI, 0.48-1.25)	RR, 0.94 (95% CI, 0.56-1.58)
High RoB	RoM, 0.66 (95% CI, 0.45-0.97)	RR, 1.02 (95% CI, 0.66-1.57)	RR, 1.81 (95% CI, 0.25-13.19)
$P_{interaction}$	.38	.41	.53
Credibility	Very low	Very low	Very low
Follow-up for intervention			
<3 mo	RoM, 0.81 (95% CI, 0.60-1.09)	RR, 0.87 (95% CI, 0.56-1.34)	RR, 0.95 (95% CI, 0.57-1.56)
≥3 mo	RoM, 0.64 (95% CI, 0.38-1.09)	RR, 0.78 (95% CI, 0.33-1.80)	RR, 4.20 (95% CI, 0.19-92.86)
$P_{interaction}$	.45	.82	.35
Credibility	Very low	Very low	Very low
Comparator			
Water baths	RoM, 0.79 (95% CI, 0.59-1.05)	RR, 0.91 (95% CI, 0.67-1.25)	RR, 0.98 (95% CI, 0.60-1.61)
No water baths	RoM, 0.68 (95% CI, 0.37-1.25)	RR, 0.46 (95% CI, 0.15-1.40)	Not estimable
$P_{interaction}$	.68	.25	N/A
Credibility	Very low	Very low	Very low
Regimented TCS			
No TCS	RoM, 0.79 (95% CI, 0.48-1.30)	RR, 0.73 (95% CI, 0.40-1.34)	RR, 1.11 (95% CI, 0.47-2.61)
TCS	RoM, 0.72 (95% CI, 0.55-0.94)	RR, 0.99 (95% CI, 0.66-1.51)	RR, 1.00 (95% CI, 0.38-2.65)
$P_{interaction}$	.76	.41	.87
Credibility	Very low	Very low	Very low
Timing of bath			
5-10 min	RoM, 0.79 (95% CI, 0.59-1.05)	RR, 0.91 (95% CI, 0.67-1.25)	RR, 0.98 (95% CI, 0.60-1.61)
10-15 min	RoM, 0.68 (95% CI, 0.37-1.25)	RR, 0.46 (95% CI, 0.15-1.40)	Not estimable
$P_{interaction}$	.68	.25	N/A
Credibility	Very low	Very low	Very low
Frequency of bath			
1 × -2 × /wk	RoM, 0.71 (95% CI, 0.55-0.92)	RR, 1.00 (95% CI, 0.74-1.36)	RR, 1.14 (95% CI, 0.45-2.89)
3 × /wk	RoM, 0.85 (95% CI, 0.49-1.47)	RR, 0.43 (95% CI, 0.07-2.64)	RR, 1.09 (95% CI, 0.34-3.51)
$P_{interaction}$	.56	.37	.96
Credibility	Very low	Very low	Very low
Emollient			
Emollient use	RoM, 0.77 (95% CI, 0.59-1.02)	RR, 0.83 (95% CI, 0.58-1.18)	RR, 0.98 (95% CI, 0.60-1.61)
No emollient use	RoM, 0.61 (95% CI, 0.02-20.84)	RR, 1.25 (95% CI, 0.49-3.19)	Not estimable
$P_{interaction}$	.89	.42	N/A
Credibility	Very low	Very low	Very low
History of bacterial infection			
No history	RoM, 0.79 (95% CI, 0.61-1.04)	RR, 0.81 (95% CI, 0.53-1.23)	RR, 0.95 (95% CI, 0.57-1.56)
History	RoM, 0.51 (95% CI, 0.17-1.56)	RR, 1.01 (95% CI, 0.64-1.60)	RR, 4.20 (95% CI, 0.19-92.86)
$P_{interaction}$	.45	.48	.35
Credibility	Very low	Very low	Very low

Abbreviations: Abx, antibiotic; CI, confidence interval; EASI, Eczema Area Severity Index; N/A, not available; RoB, risk of bias; RoM, ratio of means; RR, risk ratio; TCS, topical corticosteroid.

eTable 5
Sample size and power calculations for future bleach bath RCTs

Between-group difference in clinician-reported severity
Assumptions:
1. Common SD in both groups
2. 1:1 randomization
3. No loss to follow-up
4. Full adherence
Statistic: between-group difference comparison of means by *t* test
Hypotheses: Ho: m2 = m1 vs Ha: m2 ! = m1
Median severity of included studies (moderate-severe, EASI = 27.57)

Alpha	Power	N	N1	N2	Delta	m1	m2	SD
0.05	0.8	122	61	61	−6.06	27.57	21.51	11.76
0.05	0.9	162	81	81	−6.06	27.57	21.51	11.76
0.05	0.95	198	99	99	−6.06	27.57	21.51	11.76

Severe (EASI = 40)

Alpha	Power	N	N1	N2	Delta	m1	m2	SD
0.05	0.8	60	30	30	−8.8	40	31.2	11.76
0.05	0.8	94	47	47	−8.8	40	31.2	15
0.05	0.8	166	83	83	−8.8	40	31.2	20
0.05	0.9	78	39	39	−8.8	40	31.2	11.76
0.05	0.9	126	63	63	−8.8	40	31.2	15
0.05	0.9	220	110	110	−8.8	40	31.2	20
0.05	0.95	96	48	48	−8.8	40	31.2	11.76
0.05	0.95	154	77	77	−8.8	40	31.2	15
0.05	0.95	272	136	136	−8.8	40	31.2	20

Mild (EASI = 10)

Alpha	Power	N	N1	N2	Delta	m1	m2	SD
0.05	0.8	900	450	450	−2.2	10	7.8	11.76
0.05	0.8	418	209	209	−2.2	10	7.8	8
0.05	0.8	166	83	83	−2.2	10	7.8	5
0.05	0.9	1204	602	602	−2.2	10	7.8	11.76
0.05	0.9	558	279	279	−2.2	10	7.8	8
0.05	0.9	220	110	110	−2.2	10	7.8	5
0.05	0.95	1488	744	744	−2.2	10	7.8	11.76
0.05	0.95	690	345	345	−2.2	10	7.8	8
0.05	0.95	272	136	136	−2.2	10	7.8	5

Proportion to achieve 50% improvement
Assumptions:
1. 1:1 randomization
2. No continuity correction
3. No loss to follow-up
4. Full adherence
Estimated sample sizes for a 2-sample proportions test using Pearson's χ^2 test
Hypotheses: H_o: p2 = p1 vs H_a: p2 ! = p1
X^2

Alpha	Power	N	N1	N2	Delta	p1	p2
0.05	0.8	610	305	305	0.1012	0.2248	0.3259
0.05	0.9	816	408	408	0.1012	0.2248	0.3259
0.05	0.95	1008	504	504	0.1012	0.2248	0.3259

Abbreviations: EASI, Eczema Area Severity Index; RCT, randomized controlled trial.