

Accepted for Publication: December 10, 2009.

Author Affiliations: Department of Dermatology, University of Nottingham, Nottingham, England (Drs Langan and Williams); Dermatology Department, Technical University Dresden, Dresden, Germany (Dr Schmitt); University Medical Centre, Groningen, the Netherlands (Dr Coenraads); Department of Dermatology, University Hospital Malmö, Malmö, Sweden (Dr Svensson); and Swiss Paraplegic Research, Nottwil, Switzerland, and German Cochrane Centre, University Medical Centre Freiburg, Freiburg, Germany (Dr von Elm).

Correspondence: Sinéad Langan, PhD, Centre of Evidence-Based Dermatology, C Floor, South Block, Queen's Medical Centre, Nottingham NG 2UH, England (sinead.langan@nottingham.ac.uk).

Author Contributions: Dr Langan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Langan, Schmitt, Svensson, von Elm, and Williams. *Acquisition of data:* Langan, Schmitt, and Coenraads. *Analysis and interpretation of data:* Langan, Schmitt, Coenraads, Svensson, and von Elm. *Drafting of the manuscript:* Langan, Schmitt, and Svensson. *Critical revision of the manuscript for important intellectual content:* Coenraads, Svensson, von Elm, and Williams. *Statistical analysis:* Langan and von Elm. *Study supervision:* Svensson and Williams.

Financial Disclosure: None reported.

EDEN Group Members: Jan-Nico Bouwes Bavinck, MD, PhD; Pieter-Jan Coenraads, MD, PhD, MPH; Thomas Diepgen, MD, PhD; Peter Elsner, MD, PhD; Ignacio García-Daval, MD, MSc, PhD; Jean Jacques Grob, MD, PhD; Sinéad Langan, MD, MSc, PhD; Luigi Naldi, MD; Tamar Nijsten, MD, PhD; Jochen Schmitt, MD, MPH; Åke Svensson, MD, PhD; and Hywel Williams, MSc, PhD, FRCP.

Additional Contributions: The EDEN steering group provided useful discussions and reviewed the study checklists.

REFERENCES

1. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med*. 2007;4(10):e296.
2. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology*. 2007;18(6):800-804.
3. Altman DG, Schulz KF, Moher D, et al; CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med*. 2001;134(8):663-694.
4. Institute of Scientific Information. *Journal Citation Report 2007*. New York, NY: Thomson Reuters; 2008.
5. von Elm E, Moher D, Little J; STREGA collaboration. Reporting genetic association studies: the STREGA statement. *Lancet*. 2009;374(9684):98-100.
6. Williams HC, Seed P. Inadequate size of "negative" clinical trials in dermatology. *Br J Dermatol*. 1993;128(3):317-326.
7. Pocock SJ, Collier TJ, Dandreo KJ, et al. Issues in the reporting of epidemiological studies: a survey of recent practice. *BMJ*. 2004;329(7471):883.
8. Yoon U, Knobloch K. Quality of reporting in sports injury prevention abstracts according to the CONSORT and STROBE criteria—an analysis of the World Congress of Sports Injury Prevention in 2005 and 2008 [published online July 26, 2009]. *Br J Sports Med*. doi:10.1136/bjsm.2008.053876.
9. Fung AE, Palanki R, Bakri SJ, Depperschmidt E, Gibson A. Applying the CONSORT and STROBE statements to evaluate the reporting quality of neovascular age-related macular degeneration studies. *Ophthalmology*. 2009;116(2):286-296.
10. Müller M, Egger M. Strengthening the reporting of observational epidemiology (STROBE) in sexual health. *Sex Transm Infect*. 2009;85(3):162-164.
11. Adetugbo K, Williams H. How well are randomized controlled trials reported in the dermatology literature? *Arch Dermatol*. 2000;136(3):381-385.
12. Alvarez F, Meyer N, Gourraud PA, Paul C. CONSORT adoption and quality of reporting of randomized controlled trials: a systematic analysis in two dermatology journals. *Br J Dermatol*. 2009;161(5):1159-1165.
13. Bigby M, Stern RS, Bigby JA. An evaluation of method reporting and use in clinical trials in dermatology. *Arch Dermatol*. 1985;121(11):1394-1399.
14. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA*. 1996;276(8):637-639.
15. Rennie D. How to report randomized controlled trials: the CONSORT statement. *JAMA*. 1996;276(8):649.
16. Moher D, Jones A, Lepage L; CONSORT Group (Consolidated Standards for Reporting of Trials). Use of the CONSORT statement and quality of reports of randomized trials: a comparative before-and-after evaluation. *JAMA*. 2001;285(15):1992-1995.

EVIDENCE-BASED DERMATOLOGY: RESEARCH COMMENTARY

Bleach Baths to Reduce Severity of Atopic Dermatitis Colonized by *Staphylococcus*

Fiona E. Craig, MBBS, MRCP(UK); Emma V. Smith, MBChB, MRCP; Hywel C. Williams, MSc, PhD, FRCP; Departments of Dermatology, Aberdeen Royal Infirmary, Aberdeen, Scotland (Dr Craig), and Singleton Hospital, Swansea, Wales (Dr Smith); and Centre of Evidence-Based Dermatology, University of Nottingham, King's Meadow Campus, Nottingham, England (Dr Williams)

Commentary on: Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity

Huang JT, Abrams M, Tiougan B, et al

Pediatrics. 2009;123(5):e808-e814

Question: Does suppression of *Staphylococcus aureus* growth with sodium hypochlorite (bleach) baths and intranasal mupirocin improve atopic dermatitis (AD) severity?

Design: A 3-month, investigator-blinded, placebo-controlled, randomized controlled trial (RCT).

Setting: Pediatric dermatology clinic at the Children's Memorial Hospital, Chicago, Illinois.

Participants: Thirty-one participants aged 6 months to 17 years with moderate to severe AD and clinical signs of bacterial infection were randomized. Fifteen were assigned to receive active treatment and 16 to receive placebo. At baseline, the treatment group had higher mean Eczema

Area and Severity Index (EASI) scores and a greater proportion of body surface area (BSA) affected. Other demographics were similar for both treatment groups.

Methods/Interventions: All participants had provided samples for baseline bacterial cultures of the worst infected skin lesion and from the nares. They then all received cephalexin hydrochloride, 50 mg/kg/d, for 2 weeks prior to commencing treatment. Participants were instructed to add 0.5 cup (0.12 L) of 6% bleach (treatment group) or water (placebo group) to a full bath of water and to bathe in this solution twice weekly for 3 months. Participants were also asked to apply mupirocin ointment (treatment group) or petroleum ointment (placebo group) intranasally for 5 consecutive days, once per month for 3 months. The authors acknowledged the fact that the odor of bleach baths meant that participants did not remain blinded to their treatment allocation and have hence described this as a single-blind study.

Main Outcome Measures: The primary outcome measure was the EASI score. Other outcomes included the proportion of BSA affected, Investigator's Global Assessment (IGA) scores, results from bacterial cultures of the skin and nares at 1 and 3 months, adverse events, and compliance with bath intervention and nasal ointments.

Results: At 1 month, the treatment group achieved a 10.4-point reduction in EASI score from baseline compared with a 2.5-point reduction in the placebo group ($P=.02$). At 3 months, this difference was more significant, with a 15.3-point reduction in EASI score in the treatment group vs a 3.2-point reduction in the placebo group ($P=.004$). A subanalysis of EASI scores according to body location showed a significant difference in reduction of EASI scores in bath-submerged sites (upper limbs, trunk, lower limbs) between the 2 groups at 3 months (-4.94 in the treatment group vs -0.88 in the placebo group; $P<.001$), but not in the nonsubmerged sites (head and neck).

Participants in the treatment group also showed a greater mean reduction in the proportion of BSA affected at both 1 and 3 months. The authors state that participants in the treatment arm had significantly lower IGA scores at 1 month ($P=.02$) but that the difference in IGA scores at 3 months was not significant (no actual mean IGA values were reported). At baseline, cultures from the skin and nares yielded *S aureus* in 87% and 81% of participants, respectively. At 3 months, the proportion of participants with positive cultures was unchanged.

Conclusion: Chronic use of diluted bleach baths with intermittent intranasal application of mupirocin ointment decreases clinical severity of AD in patients with clinical signs of secondary bacterial infections without increasing resistant strains.

Comment

Study Strengths: We applaud the authors for performing a full-scale RCT as a means of following up their hunch that the addition of bleach to bathwater might help children with infected AD. We also commend their efforts in attempting to blind the participants and investigators as far as possible. The differences observed between the 2 groups in EASI score and proportion of BSA involved

seem to have been consistent at 1 and 3 months. The demonstration that decreases in severity were confined to submerged areas of the skin also might lend support to the argument that the improvements were due to the submersion in bath water containing bleach.

Quality of Reporting: Randomization was reported as "generated by a statistician" (page e809), but the method used is not described. It is also unclear how the randomization sequence was subsequently concealed from the recruiting investigators. Blinding was well explained, although it was impossible to blind the study participants because of the smell of bleach. It is unlikely that investigators became unblinded when conducting their assessments, unless they chatted with the participants. The drop-out rates in this small study were considerable; only 9 of 15 participants enrolled into the treatment arm were followed up at 3 months. The authors assert that in several cases parents in the treatment arm withdrew consent because of considerable improvement in their child's condition. The authors state that they performed an intention-to-treat analysis, as is recommended in the CONSORT guidelines for the reporting of RCTs.¹ However, the data from their participant flow diagram and the main efficacy results suggest that this was not performed, because 25 of 31 randomized participants were included in the main analysis evaluated at 1 month and 22 of 31 participants at 3 months. The study was stopped early because it had taken the study team 2 years to recruit 31 participants with clinically infected AD compared with an initial target sample size of 40 participants (or 48 as specified in the original trial registration²).

Baseline Differences: The primary end points were change in EASI score between the 2 interventions at 1 and 3 months. The difference in change of EASI score between the 2 treatments was 7.9 points in favor of bleach and mupirocin at 1 month, based on 25 participants ($P=.02$, but no confidence intervals were given), and 12.1 points at 3 months based on 22 participants ($P=.004$; no confidence intervals were given). It is important to note that EASI scores were different in the 2 groups at baseline (26.9 in the treatment group and 17.7 in the placebo group in participants who were treated for at least 1 month). It is not stated if any adjustment for baseline severity was made for the main analysis, and the lower scores in the control group mean there is less potential for change in these individuals. Another possible explanation for the modest differences seen between the treatment groups is the phenomenon of regression to the mean (ie, a tendency of participants with fluctuating disease to return to a lower disease severity value during the course of the study). Although all had clinically infected AD at enrollment and were treated for 2 weeks with cephalexin, imbalances in the proportion of participants with recurrent infected AD at baseline, which was not reported, could have accounted for the main results in such a small study.

Use of Topical Corticosteroids: Another concern is that the amount of cotreatment (ie, topical anti-inflammatory medication and emollient) was not reported in the 2 study groups. It is therefore possible that the amount

of cotreatments used differed between the 2 groups. Given that participants were unblinded to the intervention (because they could smell the bleach in the bottles), there may have been a potential source of performance bias introduced here. It is also possible that bleach-related xerosis could have occurred, necessitating increased emollient use in this group.

Inconsistencies With the Prespecified Trial Protocol:

One of the issues in interpreting this study is to determine the clinical relevance of a difference of 8 points on the EASI scale at 1 month and 12 points at 3 months. Here, the IGA score could have been very helpful, that is, the proportion of participants with an IGA score of 0 (clear) or 1 (almost clear). Disappointingly, this categorical measure is not presented in the results, and readers are simply told that at 3 months “only a trend toward lower IGA scores (page e811)” was present. On examination of the original trial protocol for prespecified secondary outcomes, it is clearly stated that the team planned to analyze the proportion of participants with an IGA score of clear or almost clear, but the data are not presented in this report. Inspection of the trial registry protocol also revealed that change in itch reported on a visual analog scale by participants and their families was originally a secondary outcome, but such patient-reported outcomes are completely missing from the final trial report. The subgroup analysis of submerged vs head and neck body sites was not prespecified in the registered protocol, so care should be taken when interpreting such post hoc findings, especially because a comparison of just the head and neck (which comprise 10% of the EASI score) would have less power to determine a true difference than a comparison of the rest of the body sites.

Safety: One of 9 participants experienced itching and irritation of the skin with the use of the bleach baths. Although the addition of bleach to a bathtub of water sounds safe, it is possible that confusion with concentrations or volumes could result in skin irritation or superficial bleach burning.

Antibiotic Resistance: The study introduction highlights the possibility that increasing levels of staphylococcal resistance (particularly methicillin-resistant *S aureus* [MRSA]) may result from treatment of AD with topical or systemic antibiotics. However, the study intervention involved continued use of intranasal mupirocin (a topical antibiotic), which may in itself promote antibiotic resistance. The authors state that no resistance to mupirocin was seen following the intervention but do not comment on resistance to other commonly used antibiotics. They acknowledge that the prevalence of MRSA among participants did not change following the intervention, and yet there is considerable focus on the issue of MRSA in the discussion and abstract. Overall, this aspect adds very little to the implications of the study.

What Role Does *S aureus* Play in AD? There is little dispute that *S aureus* colonization is very common in AD,

yet its role in driving disease severity is still unclear. A recent systematic review of 21 RCTs of antistaphylococcal interventions in AD found that several products reduced *S aureus* numbers on the skin, but none showed a clinically worthwhile benefit in eczema severity.³ The title of the study discussed herein clearly suggests that the decrease in AD severity is due to treatment of *S aureus* colonization. However, the results indicate that the proportions of participants with AD colonized at the study outset were unchanged following intervention, so it is difficult to see how the changes in disease severity could be attributed to reduction in bacterial colonization, which is implied by the authors to be the rationale for clinical improvement. Furthermore, quantitative data on degree of colonization are not included. This study design combines 2 different interventions in the active group, making it difficult to determine the true treatment effect of either intervention alone. A more informative study design might have been a 4-arm study, comparing each active intervention alone with both combined and with placebo, to make a clearer comparison of treatment effects. It is also worth noting that all participants initially received oral antibiotics, which somewhat limits the external validity of this study.

Bottom Line: It is good to see a trial of a simple, cheap intervention that might help children with infected AD. However, it is unclear if the differences in favor of topical nasal mupirocin and bleach baths shown in this study are due to differences in baseline severity, differences in use of cotreatments during the study, or a failure to undertake an intention-to-treat analysis. We will not be changing our practice on the basis of these findings for most of our patients with AD. We welcome an additional larger and longer term study of a similar approach with a prespecified publicly accessible protocol that allows for baseline differences with outcomes such as global improvement and prevention of disease flares that can be widely interpreted by health care practitioners.

Correspondence: Fiona E. Craig, MBBS, MRCP(UK), Department of Dermatology, Aberdeen Royal Infirmary, Forsterhill Road, Aberdeen AB25 2ZN, Scotland (fionacraig1@nhs.net).

Financial Disclosure: None reported.

Additional Contributions: John Batchelor, BMedSci, BM, BS, MRCP, John Ingram, MBChB, MRCP, and Gemma Minifie provided critical appraisal of the original article.

REFERENCES

1. Begg C, Cho MK, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA*. 1996;276(8):637-639.
2. The impact of treating *Staphylococcus aureus* infection and colonization on the clinical severity of atopic dermatitis. <http://www.clinicaltrials.gov/ct2/show/NCT00179959?term=NCT00179959&rank=1>. Accessed June 2, 2009.
3. Birnie AJ, Bath-Hextall FJ, Ravenscroft JC, Williams HC. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema. *Cochrane Database Syst Rev*. 2008;(3):CD003871. doi:10.1002/14651858.CD003871.pub2.