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ABSTRACT

BACKGROUND: Studies evaluating bathing frequency in pediatric atopic dermatitis (AD) are limited.

Parents of children with AD often receive conflicting information, leading to frustration and confusion.

OBJECTIVE: To evaluate efficacy of twice-daily, soaking baths, followed by immediate application of an occlusive moisturizer (i.e. soak-and-seal [SS]), versus twice-weekly SS baths, in the acute management of pediatric AD.

METHODS: We conducted a randomized, single-blind, crossover-controlled trial comparing frequent versus infrequent SS baths, in children 6 months to 11 years of age with moderate-to-severe AD.

Children were randomized 1:1 into 2 groups: Group 1 underwent twice-weekly SS baths, for 10-minutes or less, over 2-weeks ("dry method" - DM) followed by twice-daily SS baths, for 15-20 minutes, over 2-weeks ("wet method" - WM). Group 2 did the inverse. Patients received the same moisturizer, cleanser, and low-potency topical corticosteroid (TCS). Primary outcome was AD severity evaluated using SCORing Atopic Dermatitis (SCORAD) index. Caregiver assessment of AD severity (Atopic Dermatitis Quickscore – ADQ), quality of life, *Staphylococcal aureus* colonization, skin hydration, moisturizer and TCS usage were assessed.

RESULTS: Of the 63 children screened, 42 fulfilled inclusion criteria and were randomized. Forty (95%) completed the study. WM decreased SCORAD by 21.2 compared with DM (95% CI, 14.9 to 27.6; $P<0.0001$). Secondary analysis showed a greater than 30% SCORAD improvement for WM versus DM (McNemar's $\chi^2=8.83$, $df=1$, $p=0.0030$). SCORAD correlated with ADQ ($r=0.66$), and ADQ also showed significant improvement with WM decreasing ADQ by 5.8 (95% CI, 1.8 to 9.7). No other secondary endpoints showed significance.

CONCLUSIONS: As an acute treatment intervention, WM is superior to DM at improving disease severity in moderate-to-severe pediatric AD.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT03397979

NAME OF TRIAL REGISTRY: Twice-daily versus twice-weekly soak-and-seal baths in pediatric atopic dermatitis: A randomized, single-blinded, prospective, crossover-controlled trial

81

82 **HIGHLIGHT BOX**

83 **What is already known about this topic?** Moisturizers and topical corticosteroids (TCS) are the
84 mainstay of therapy for atopic dermatitis (AD), but studies on optimal bathing frequency are limited.

85 **What does this article add to our knowledge?** Added to standard-of-care TCS and moisturizer in
86 pediatric moderate-to-severe AD, twice-daily soak-and-seal (SS) baths over two weeks demonstrated a
87 statistically and clinically significant reduction in severity of symptoms, versus twice-weekly SS baths
88 over two weeks.

89 **How does this study impact current management guidelines?** Our findings support twice-daily SS baths,
90 as a safe and effective acute treatment intervention, to improve disease severity in children with
91 moderate-to-severe AD.

92

93 **Key words:** Atopic dermatitis; Eczema; Bathing; Baths.

94

95 **Abbreviations used:**

96 AD – Atopic Dermatitis

97 SS – Soak-and-seal

98 DM – Dry method

99 WM – Wet method

100 TCS – Topical corticosteroid

- 101 SCORAD – SCORing Atopic Dermatitis
- 102 PCPs – Primary care physicians
- 103 SC – Stratum corneum
- 104 TEWL – Trans-epidermal water loss
- 105 WWT – Wet wrap therapy
- 106 *S. aureus* – *Staphylococcal aureus*
- 107 ADQ – Atopic Dermatitis Quickscore
- 108 IDQOL – Infant’s Dermatitis Quality of Life
- 109 CDLQI – Children’s Dermatology Life Quality Index
- 110 DFI – Dermatitis Family Impact
- 111 ITT – Intention-to-treat
- 112 LOCF – Last-observation-carried-forward
- 113 MCID – Minimal-Clinically-Important-Difference
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INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin condition affecting between 15-30% of children worldwide¹⁻³. It is characterized by skin barrier dysfunction and immune dysregulation^{4,5}. Despite its significant prevalence, few studies have evaluated best bathing practices, including bathing frequency, in the management of pediatric AD. Consequently, AD guidelines remain inconsistent⁶⁻¹².

Parents of children with AD often receive conflicting information regarding bathing frequency. We published data demonstrating primary care physicians (PCPs) recommend daily bathing <50% of the time, while specialists (i.e. allergists-immunologists/pediatric dermatologists), recommend daily bathing >50% of the time¹³. This finding supported our previous survey of 354 parents of children with AD, reporting specialists were more likely to recommend daily bathing than PCPs; conflicting advice causing frustration and confusion¹⁴. Recently, we published a literature review revealing that the few studies published on bathing frequency were limited by design flaws, but suggest a slight advantage favoring frequent bathing¹⁵.

Our understanding of the pathophysiology of AD has advanced significantly. A healthy stratum corneum (SC) has a water content of at least 10%. Xerosis of the skin, a typical feature of AD, occurs when SC water content drops below 10% and enzymatic processes become impaired, leading to abnormal skin desquamation and corneocyte accumulation¹⁶. Skin barrier defects play a fundamental role in the development and ongoing pathology of AD. The SC functions as a permeability barrier to mitigate trans-epidermal water loss (TEWL)¹⁷. SC abnormalities, such as defects in filaggrin expression, extracellular

lipid production and arrangement, and corneocyte intercellular junctions, all play a role in the defective barrier that leads to TEWL, seen in both lesional and non-lesional AD skin. Allergens, irritants, and infective agents can more easily penetrate the defective skin, leading to inflammation. This inflammation leads to further skin barrier abnormalities, as type 2 (T2) inflammation, characterized by the production of the cytokines interleukin-4 and 13, seems to subvert the normal expression of filaggrin, lipid production, and intercellular junction formation^{16,18}. Thus, a vicious cycle occurs where skin barrier defects beget T2 inflammation which begets further skin barrier defects.

It is unclear what role bathing frequency plays in this cycle, or in AD control. Data suggests occlusive wet-wrap therapy (WWT) for children with moderate-to-severe AD is effective acutely¹⁹⁻²¹. Soak-and-smear (or soak-and-seal) (SS), whereby patients soak in the tub for at least 10-15 minutes, immediately pat dry, then apply an occlusive (sometimes medicated) emollient, has also been shown to be effective acutely²²⁻²⁵. Considering the importance of skin hydration and TEWL in the pathophysiology of AD, and considering SS bathing may mimic WWT by enhancing penetration of topical agents and preventing water loss, we hypothesized that frequent SS bathing may be more effective than restricting bathing in the management of pediatric AD (which is commonly recommended by some health care practitioners^{13,14}).

Our objective was to compare the effectiveness of twice-daily, 15-20-minute, SS baths, as an acute treatment intervention, versus twice-weekly, 10 minutes or less, SS baths, on AD severity. For simplicity, we define the former as the wet method (WM), and the latter as the dry method (DM). We also sought to quantify AD medication burden, quality of life (QoL), skin hydration status, and colonization density of

Staphylococcus Aureus (S. aureus), between WM and DM. We evaluated *frequency* of SS bathing and not the efficacy of the SS method alone, which has previously been shown to be effective²⁶⁻³¹.

METHODS

Study Design

We performed a randomized clinical study with a single-blind, crossover design, at a hospital-affiliated allergy-immunology practice in Maine, USA. The institutional review board of Maine Medical Center approved the protocol which conformed to the principles of the Declaration of Helsinki³². Parents/legal guardians provided written informed consent. Study subjects ages 7-11 provided written informed assent after caregivers consented to the children's participation.

Participants

Patients ages 6 months to 11 years with physician-diagnosed AD, according to the criteria of Hanifin and Rajka (Acta Derm Venereol (Stockh) 1980; Suppl 92: 44-47), having a SCORing Atopic Dermatitis (SCORAD) index of at least 25 or higher (i.e. moderate-to-severe), were recruited from September 27, 2011 to March 21, 2017. Follow-up was completed on April 5, 2017. Exclusion criteria included patients with suspected or established primary immunodeficiency, patients receiving systemic corticosteroids, ultraviolet light therapy, immunotherapeutic agents, and/or anti-infective drugs less than one month from study onset. Patient's whose SCORAD score dropped below 25 (i.e. mild AD) after the run-in week were excluded from randomization.

Randomization and Masking

After a 1-week run-in, participants were randomly assigned to two groups in a 1:1 ratio. Group 1 underwent twice-weekly SS baths (for 10 minutes or less) for 2 weeks (i.e. DM) followed by twice-daily

SS baths (for 15-20 minutes) for 2 weeks (i.e. WM), and Group 2 did the inverse. A nurse randomized patients by presenting caregivers with two sealed envelopes from which to choose, each containing a written #1 or #2. The chosen number dictated group assignment. This nurse also provided and reviewed the corresponding bathing logs for each group, which explicitly explained the technique and frequency of the SS method. A single physician, masked to group assignment, assessed the primary outcome.

Procedures

This study involved 4 visits over 5 weeks (Figure 1). At visit 1, a detailed history/physical was conducted and patients were screened using the SCORAD index, the primary endpoint³³. Allergy skin prick testing was performed, if appropriate. The nurse provided families general AD education and allergen avoidance information based on skin prick results. Caregivers assessed their child's AD severity using the Atopic Dermatitis QuickScore (ADQ; range 0-70; higher scores indicating worse symptoms)³⁴. For patients ≤ 4 years of age, caregivers assessed their child's QoL using the Infant's Dermatitis Quality of Life Index survey (IDQOL; range 0-30; higher scores indicating worse QoL)³⁵. Children 4 to 11 assessed their own QoL using The Children's Dermatology Life Quality Index questionnaire (CDLQI; range 0-30; higher scores indicating more QoL impairment)³⁶. Caregivers also assessed the QoL impact of AD on the whole family using the Dermatitis Family Impact questionnaire (DFI; range 0-30; higher scores indicating greater impact on family)³⁷

After visit 1, patients discontinued previous medications, moisturizers, and cleansing products and underwent a 1-week run-in period. All patients received Vanicream Free & Clear Liquid cleanserTM (to be used as needed), class VI topical corticosteroid (TCS) desonide 0.05% ointment (to be used once to twice per day on affected areas as needed), and the same non-medicated emollient/moisturizer (VanicreamTM to be used twice a day at a minimum, and/or after soaking baths). Baseline weight in

grams for both TCS and moisturizer were measured. To control for baseline bathing frequency, bathing during run-in week was every other day for 10 minutes or less (timers were provided). The application of topicals was done in an SS fashion only on bath days; patients could apply topicals on non-bath days per their routine.

Patients returned for visit 2 after the run-in week. SCORAD along with TCS and moisturizer usage were measured. Patients who remained moderate-to-severe based on SCORAD were randomized as described. Randomized patients received a baseline skin culture for *S. aureus* (relative quantities: 1+ rare, 2+ few, 3+ moderate, 4+ many), collated from the most affected area, and baseline SC hydration status measured using the noninvasive NOVA Dermal Phase Meter (DPM 9003 NOVA Technology, Portsmouth, NH, U.S.A.). DPM measurements were taken as a mean value of 3 recordings from the volar forearm and mid-thigh region. The DPM 9003 meter indirectly determines SC hydration status via impedance-based capacitance³⁸. Caregivers assessed ADQ, IDQOL, and DFI. Patients assessed CDLQI.

Visit 3 occurred at the end of the first two treatment weeks. SCORAD, ADQ, IDQOL, DFI, CDLQI, skin cultures, skin hydration status, and TCS and moisturizer usage were assessed as described above. Skin cultures were gathered from the same locations. Patients then crossed-over to the opposite treatment arm for 2 weeks.

Visit 4 occurred at the end of the final two treatment weeks. Primary and secondary outcomes were assessed as above.

The research coordinator called caregivers each week throughout their participation in the study.

Caregivers brought bathing logs to each visit for review.

Outcomes

The primary outcome was the change in SCORAD during each 2-week treatment phase (visit 2 to 3 and visit 3 to 4). Secondary outcomes included changes in ADQ, QoL measures (IDQOL, DFI, and CDLQI), amount of TCS and moisturizer used, skin hydration status, and *S. aureus* colonization density during each treatment phase.

Statistical Analysis

Efficacy analyses were performed using the intent-to-treat (ITT) population, predefined as all patients who were randomized. Outcomes analyses were performed using the method for a continuous outcome in a 2x2 crossover trial. A repeated measures ANOVA model with period, treatment, and treatment by period interaction effects was used to model the difference in score from each visit versus baseline. Data from all patients was used although later visit data was missing for two patients that were lost to follow-up. To evaluate whether one method showed a greater than 30% reduction in SCORAD or ADQ, this binary outcome in this paired sample set was tested using a McNemar's chi-squared test. Data were analyzed using R (version 3.4.2) for data management, basic statistical testing, and the McNemar's tests. Mixed models were fit using SAS Enterprise Guide version 7.15 using Proc Mixed.

Sample Size Calculation

Despite lack of consensus, some studies consider 30% reduction in symptoms to be clinically significant^{39,40} (initial primary outcome). Consequently, initial target sample size of 67 was selected to have 80% power to detect a difference in proportions of 30%, when the proportion of discordant pairs is

expected to be 80%, using a McNemar's chi-squared test at a two-sided significance level of 0.05. Therefore, enrollment target was 74 to allow for an approximate ~10% drop-out rate. However, due to a higher than expected pre-randomization attrition rate, slower than expected enrollment, and evolving understanding of what constitutes a clinically meaningful change in SCORAD⁴¹, study was stopped and we amended the protocol to have the overall difference in change in SCORAD be the primary outcome, which has higher power, and then analyzed the data with the existing cohort (n=42).

RESULTS

We recruited 63 children with moderate-to-severe AD. The attrition rate after the run-in week (pre-randomization) was 33% (21 patients). The majority (i.e. 13 of the 21 patients) did not meet inclusion criteria because the eczema severity score dropped to the mild category. Of the remaining 8 patients (13% dropout), 6 were lost to follow-up and 2 declined to participate despite meeting inclusion criteria (Figure 1). After exclusion, 42 patients were randomized into 2 groups. Ages and baseline clinical characteristics were similar between Group 1 (median age, 3.9 years; age range 6 months – 11.5 years) and Group 2 (3.5 years; 6 months – 10 years) (Table 1). One patient withdrew in Group 1 after two weeks of DM (moved out of state). Another withdrew in Group 2 during DM, for reported AD flaring. All 42 patients underwent evaluation by ITT.

Regarding AD severity, we found that WM for both groups had a greater decrease from baseline in the mean change in SCORAD than DM. Our model estimate of SCORAD treatment effect between WM and DM was 21.2 (Table 2: 95% CI; 14.9 to 27.6; $P < 0.0001$). This effect exceeded the minimal-clinically-important-difference (MCID) for SCORAD, which has been estimated to be a change of 8.7⁴¹. Since some studies consider 30% reduction in symptoms to be clinically significant, using McNemar's chi-

squared test as a secondary analysis; the number of patients that achieved a 30% response with WM (but not DM) was 23, while the number of patients that achieved a 30% response in DM (but not WM) was 6. Again, WM demonstrated a significant improvement over DM (Figure 2: $\chi^2=8.83$, $df=1$, $p=0.003$). Likewise, the decrease in ADQ for WM compared to DM was 5.8 (Table 2: 95% CI; 1.8 to 9.7) which was also statistically significant. In addition, the change in SCORAD correlated with the change in ADQ (Figure 3: $r = 0.66$). The McNemar test for ADQ however, trended similarly but did not reach significance ($p=0.061$).

With the modest sample size of this study, we were only powered to detect large changes in secondary outcomes, which we did not see in moisturizer and TCS usage, QoL, skin hydration status, or *S. aureus* colony counts (Table 2). There was a small trend toward more moisturizer usage in WM, although this difference was not statistically significant.

DISCUSSION

In this randomized trial of frequent bathing (WM) versus infrequent bathing (DM) added to standard-of-care TCS and moisturizer in children with moderate-to-severe AD, WM demonstrated a statistically and clinically significant reduction in the severity of symptoms when compared to DM as measured by SCORAD and ADQ. These data suggest that twice-daily SS baths reduce disease severity in moderate-to-severe AD.

To our knowledge, this is the first study to examine the question of bathing frequency in combination with SS, utilizing a randomized single-blind prospective crossover-controlled design. Whereas studies

evaluating bathing frequency in combination with SS are limited in number, size and quality, the efficacy of the WM approach seen in our study is consistent with previous reports^{15,17, 22-25,42-45}.

Although several potential explanations for our results exist, the most likely explanation is that the enhanced absorption of TCS and the “washing away” of potential allergens and irritants improved immune dysregulation, rather than improved skin barrier function. Evidence suggests that topical medications penetrate a hydrated SC significantly better than a dehydrated SC⁴⁶. Consequently, WM could be steroid-sparing by increasing TCS efficacy in this way; similar to the proposed mechanism of efficacy for WWT (e.g. it is common clinical practice to use a TCS more potent than desonide 0.05% ointment for moderate-severe AD flares)^{25,47-49}. Further, skin exposure to allergens can contribute to cutaneous inflammation in AD⁴⁷⁻⁴⁹. It is possible that WM may result in more effective removal of scales, crusts, allergens and irritants that contribute to this inflammation. This hypothesized “washing away” of potential allergens and irritants did not correlate with seasonal variation in efficacy. To test the effect of season, we added a term for seasons in our repeated measures ANOVA model and did not find it to be significant, either as a main effect or in interaction with other model effects ($p=0.81$ as main effect). It must be noted however, that the lack of seasonal variability might be due to the insufficient power to detect any significant difference, as the sample size for our study was small.

We also found a statistical difference in ADQ although the effect size was smaller. This could be due to the difficulty in masking caregivers/parents from the bathing of their children, and because the ADQ is less precise due to increased variability. In addition, we did not find a statistical difference in skin hydration between WM versus DM, a finding that has previously been demonstrated⁵⁰. Although the improvement in AD seen with WM does not seem related to increased SC hydration, we did not

measure TEWL, which is considered a better biomarker of skin barrier function^{16,17}. Thus, it is possible that WM improved skin barrier function^{51,52}. Those recommending infrequent bathing frequently cite that WM decreases SC hydration—we found that it does not. The xerotic effects of frequent bathing may have more to do with the use of detergents than with bathing^{50,53-56}.

QoL scores did not differ significantly between bathing groups. Interestingly, baseline QoL scores were relatively low, leaving little room for improvement. Moreover, CDLQI and SCORAD have been shown to not correlate well with each other, and may represent separate dimensions in the assessment of AD in children⁵⁷. We also noted a statistically nonsignificant small trend toward more moisturizer usage with WM, despite the fact that DM was instructed to apply moisturizer twice a day at a minimum, to balance usage of moisturizer with WM. Compliance to this instruction may have been low without the bathing cue to prompt usage, and may account for the slight increase in moisturizer usage for WM.

We did not find that WM had an impact on *S. aureus* colonization. Current practices for the management of *S. aureus* colonization and/or infections include antiseptics (particularly diluted bleach baths), topical antibiotics (including periodic intranasal mupirocin), and systemic antibiotics⁵⁸. The effects of these interventions on *S. aureus* colonization is questionable as mentioned in a recent review by Nakatsuji and Gallo⁵⁹. Emerging evidence, as mentioned in this same review, suggests that dysbiosis caused by an imbalance of *S. aureus* in relation to other commensal and potentially symbiotic organisms that normally reside in the skin, may in fact be more explanatory with regards to the activity of *S. aureus* in contributing to the pathology of AD skin. Repopulation of the skin with commensal protective strains of bacteria such as *S. epidermidis* and *S. hominis*, which have antimicrobial activity and specifically activity that diminishes *S. aureus*-mediated inflammation, may be an important mechanism to control

inflammation in AD⁶⁰. Various factors seem to influence the skin microbiome, including humidity, temperature, pH, and lipid content⁶¹. Because we did not evaluate for changes in the skin microbiome outside of the presence of *S. aureus* colonization, an alternative explanation for our findings could be that WM had an impact on one or more of these factors, possibly promoting a more balanced skin microbiome. Another reason why WM may not have impacted *S. aureus* colonization is because our trial was not powered to assess this secondary endpoint.

WM was well tolerated, and no serious adverse events were reported. There was one drop-out after visit 3 due to reported AD flaring, but since the patient never showed for the final visit of the study, we do not know the extent of this flare. (Of note, the patient's reported flare occurred during the DM phase after cross-over from the WM).

This study has several strengths, including the single-blinded prospective randomized crossover design. To eliminate interpersonal assessor variability, only one physician assessed AD severity with the validated clinical tool SCORAD. Further, results correlated with ADQ. All subjects received the same moisturizer, cleanser, and low-mid potency TCS (so as to not obscure potential differences that bathing frequency might impart). Adherence was monitored and encouraged by providing bathing logs and via direct patient phone contact⁶². Patients were specifically trained on the SS method to ensure consistency in the bathing method used. Drop-outs were low post-randomization.

Weaknesses include a small sample size, a large attrition rate pre-randomization, and lack of a wash-out phase between treatment arms. The 33% pre-randomization attrition rate among the initially screened

patients should be acknowledged, as it could lead to a selection bias that overestimates the success rate of the WM. However, pre-enrollment, there were comparable numbers of patients (in each randomization group) reporting bathing $\geq$ every other day as well as bathing $<$ every other day (Pearson's chi-squared test statistically non-significant; $P=0.26$, data not shown). Although the method (e.g. showers versus soaking baths) and duration of bathing (e.g. < 10 minutes vs. > 10 minutes, etc.) varied significantly, we do not know how many patients prior to entering the study followed the exact SS approach we recommended in our run-in week (or treatment phase of our study). Thus, one could hypothesize that, because the attrition rate was mostly due to improved AD severity (13 of the 21), and the run-in week involved a more intense SS approach as compared to what many patients were doing prior to entering the study, our results would have been further strengthened, had we not excluded mild AD, but this is uncertain. Other potential causes for pre-randomization dropout are important to mention. Eczema may have improved during the run-in week because families were more adherent to a treatment regimen, regardless of frequency or method of bathing. In addition, for the 6 patients that were lost to follow-up and the 2 that declined to participate, their parents may have felt concern for adverse events during the study, or may have felt overwhelmed with the bathing regimen required for frequent SS.

The amount of time needed for wash-out in a bathing study is not known. In addition, it has been our clinical experience that moderate-to-severe AD flaring can occur quite quickly, even shortly after a previously effective skin care bathing regimen has been discontinued. We assumed that the length of the time between visits gave sufficient time for the effects of the old treatment to be removed and replaced by the effects of the new treatment. Moreover, we wanted to keep the study length as short as possible in order to minimize drop-outs and increase adherence, and indeed there were only two drop-outs post-randomization. Taken together, we chose not to include a wash-out prior to crossover, as we

felt that a carryover effect from the bathing regimens would be less likely. Nevertheless, and unfortunately, lack of a wash-out does weaken the study design, so an important next step is to replicate this study with a larger sample size that includes a wash-out and does not exclude mild AD.

Other limitations include lack of directly observed adherence, lack of monitoring environmental factors such as temperature, humidity, or quality of water used in bathing, lack of tracking ethnicity and gender, and lack of control over caregiver bias regarding bathing (i.e. caregivers were not masked), something that would be difficult to control in this type of study without a third party individual going to families homes and conducting the baths, and removal of the caretaker from the intervention arm.

We studied a pediatric population and cannot extrapolate our results to an adult population, considering the phenotype of pediatric AD has been shown to be substantially different from long-standing disease in adults. Compared to adults, pediatric AD is characterized by increased TH2 and TH17/TH22 responses with lower TH1 activation and IFN- γ responses^{63,64}. Most of our patients (76%) were allergen-sensitized on skin prick test, as one would expect in an allergy practice. Patients with atopic eczema tend to show more allergic sensitization, more severe and persistent disease, and produce less filaggrin expression when compared to non-atopic eczema⁶⁵⁻⁶⁸. Whether these results would be consistent in a less atopic adult population is unclear.

We are unable to comment on the effect of WM without TCS, as all subjects received low potency TCS. Because TCS is considered standard-of-care therapy for AD, we did not think it was ethical to restrict TCS in this population of moderate-to-severe disease. Nevertheless, the significant clinical benefits seen

with WM over DM cannot be explained by the use of TCS or moisturizer, as there was no significant difference in usage between treatment arms.

We acknowledge that twice-daily SS bathing in the real-world can be time-consuming, making adherence difficult for families. Although adherence was high in our study, in part due to required bathing logs and direct patient phone contact, these incentives would not be present in a non-research setting. That said, our study was meant to be an acute treatment intervention in the short term (2 weeks), to be done when the patient is experiencing a moderate-to-severe flare. We chose to study twice-daily bathing over daily bathing to closer approximate the hypothesized effects of WWT. Although twice-daily bathing requires more work on the part of families, we show that its implementation is more effective than infrequent bathing, and in the short term, over two weeks in the midst of a moderate-to-severe flare, has the potential to improve eczema severity without resorting to more labor-intensive wet wraps, and without requiring more potent topical steroids.

Larger studies are needed to evaluate the role of SS bathing frequency in the treatment, as well as prevention, of AD. Mechanistic studies to evaluate how bathing impacts cutaneous inflammation and/or barrier dysfunction would also be useful. With personalized medicine at the forefront of patient care, studies are needed to evaluate what risk factors/biomarkers might predict which bathing approach is ideal for each patient (e.g. atopic versus non-atopic dermatitis).

While further studies may determine if a WM approach without TCS can reduce the risk of AD flaring long term, we found that among children 6 months to 11 years with moderate-to-severe AD, the

implementation of a WM approach, as an acute treatment intervention to standard-of-care TCS, was safe, diminished AD severity, and may have a steroid-sparing effect.

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626 **FIGURE LEGENDS:**627 **Figure 1:**

628 CONSORT diagram of the randomization and follow up of study participants through the bathing
629 regimens

630

631 **Figure 2:**

632 There were significantly more patients that achieved a 30% improvement in SCORAD with wet method
633 exclusively versus dry method exclusively ($\chi^2=8.83$, $df=1$, $p=0.003$).

634

635 **Figure 3:**

636 SCORAD change correlates with ADQ change ($r=0.66$) with the former as the primary outcome,
637 demonstrating clinical and statistical significance (see Figure 2 and Table 2).

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Table 1: Baseline (Visit 2) Characteristics of Randomized Patients by Treatment Group		
Variable^{a,b}	Group 1 (n=21)	Group 2 (n=21)
Age	3.9 (3.8)	3.5 (2.7)
SCORAD (physician assessed)	41.9 (13.7)	41.2 (13.0)
ADQ (parent assessed)	26.4 (12.8)	24.5 (10.0)
DFI (QOL - 5 & up - parent assessed) ^c	6.6 (5.0)	7.2 (4.5)
CDLQI (QOL - 5 & up - patient assessed)	5.0 (3.3)	5.6 (5.5)
IDQOL (QOL - 4 & under - parent assessed)	8.1 (4.6)	7.4 (4.0)
<i>S. aureus</i> Relative Colonization Density	2.1 (1.5)	2.0 (1.5)
MRSA Infections	3 (14.3%)	3 (14.3%)
Hydration (Volar forearm) ^{d,e}	127.2 (47.5)	125.7 (45.2)
Vanicream TM Usage (g) ^f	53.7 (62.8)	65.8 (52.6)
Desonide Usage (g) ^g	10.6 (10.6)	11.1 (7.2)
Allergen-sensitized on skin prick test	18 (85.7%)	14 (66.6%)

Abbreviations: SCORAD, SCORing Atopic Dermatitis; ADQ, Atopic Dermatitis Quickscore; QOL, Quality of Life; DFI, Dermatitis Family Impact; CDLQI, Children's Dermatology Life Quality Index; IDQOL, Infant Dermatitis Quality of Life; *S. aureus*, Staphylococcal aureus; MRSA, Methicillin Resistant Staphylococcal aureus

^a Mean (SD) or Count (%) for continuous and categorical clinical variables, respectively

^b No differences were statistically significant

^c missing for 3 individuals (2 from group 1, 1 from group 2)

^d missing for 1 individual from group 2

^e data from mid-thigh region not shown but also not statistically significant

^{f,g} missing for 2 individuals from group 2

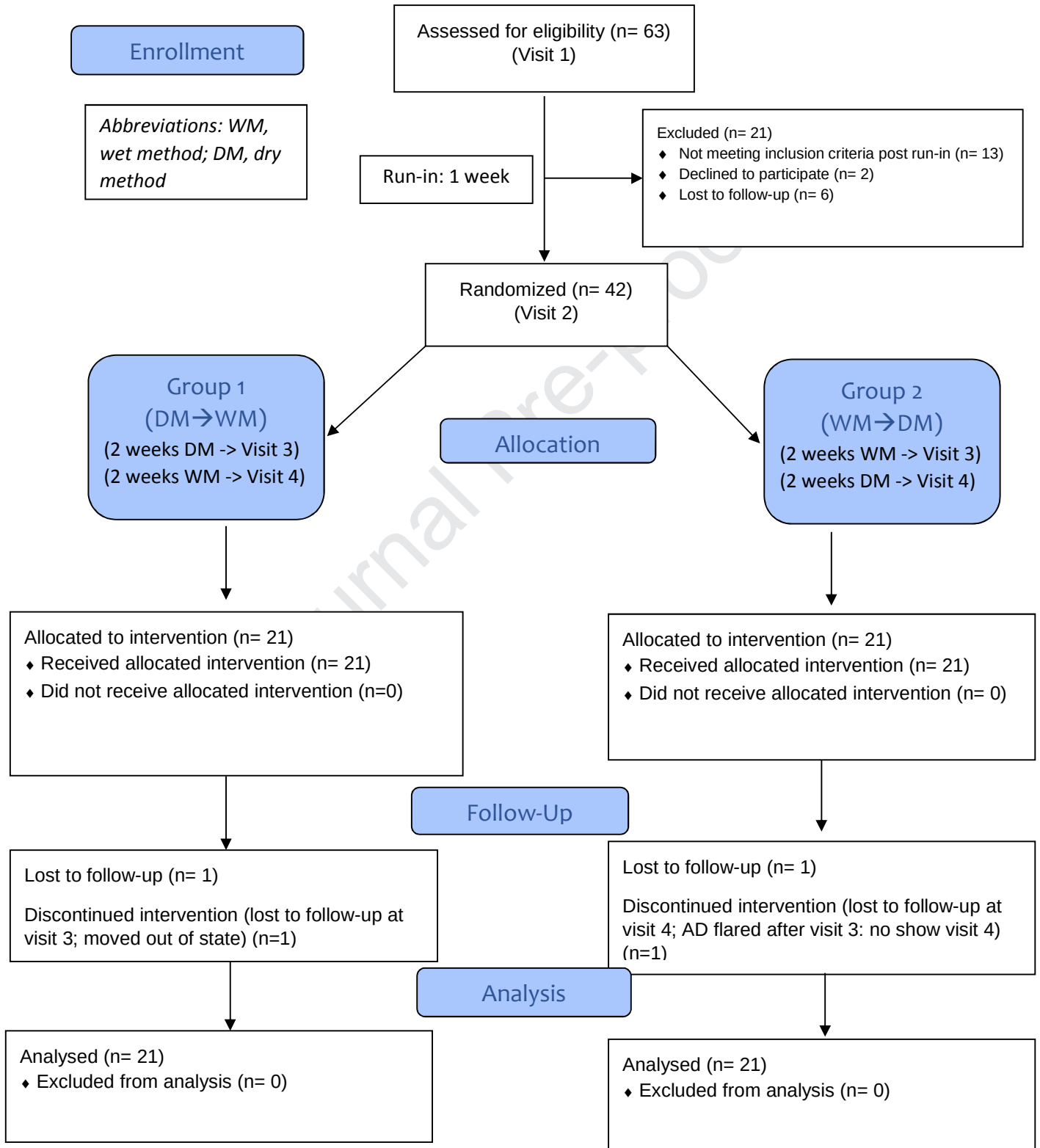
Table 2: Effect Size of Frequent (WM) vs Infrequent (DM) Bathing		
Variable	Effect Size	P-value
<i>SCORAD (physician assessed)</i>	21.23	<.0001
<i>ADQ (parent assessed)</i>	5.76	0.0052
<i>DFI^a (QOL - 5 & up - parent assessed)</i>	-0.15	0.9074
<i>CDLQI (QOL - 5 & up - patient assessed)</i>	0.04	0.9704
<i>IDQOL (QOL - 4 & under)</i>	2.03	0.1052
<i>S. aureus Relative Colonization Density</i>	0.10	0.8273
<i>Hydration (Volar forearm)^b</i>	5.00	0.5650
<i>VanicreamTM Usage^c</i>	-30.40	0.0583
<i>Desonide Usage^c</i>	-1.45	0.5181

^a missing for 3 individuals (2 from group 1, 1 from group 2)

^b missing for 1 individual (from group 2)

^c missing for 8 individuals (3 from group 1, 5 from group 2)

Figure 1. Flow Chart: randomized control crossover trial



30% Scorad Improvement