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Dr. Shanna Spring is a board-certified dermatologist in both Canada and the United States. After completing her undergraduate Bachelor of Science degree at McGill, she studied medicine at the University of Toronto. Upon completion of her MD, she moved back to her hometown of Ottawa for her residency in dermatology. An interest in pediatric dermatology sent her on a year-long fellowship to the University of California - San Francisco (UCSF) and the University of Toronto (SickKids). Now settled back in Ottawa, she splits her time between CHEO, Bruyere Hospital and The Ottawa Hospital with a continued interest in pediatric dermatology.

RETHINKING CONVENTIONS IN PEDIATRIC ATOPIC DERMATITIS

Antihistamines in atopic dermatitis

During my residency training, we were taught to encourage parents to use Benadryl® (diphenhydramine) or Atarax® (hydroxyzine) at night to help their itchy children sleep better. Parents were instructed to use higher doses than labelling on the bottle suggested, as the clinical intent was to use it for its sedating side effects rather than any sort of specific treatment for their child's atopic dermatitis.

This past year, the Canadian Society for Allergy and Clinical Immunology (CSACI) came out with a position statement on proper antihistamine use, directly in opposition to this practice.[1] First generation H1 antihistamines have side effects like sedation and impairment with decreased cognitive function. Although they may help initiate sleep, they have been shown to cause poor sleep quality. These antihistamines cross the blood brain barrier and cause significant CNS suppression. Some studies have shown a decrease in school performance in patients regularly taking this medication.[2] Previous use of first generation antihistamines has a possible association with increased ADHD symptoms in children with atopic dermatitis.[3]

Second generation antihistamines are more efficacious and safer than first generation antihistamines.[5] These second generation drugs are now our first line therapy for urticaria and rhino-conjunctivitis. There is evidence that rupatadine, one of the newer second generation antihistamines, may even have some antipruritic effects in atopic dermatitis.[4] Despite its long history of use in acute type I allergic reactions, pediatric hospital protocols for anaphylaxis no longer include oral Benadryl®. CSACI has recommended that all first generation antihistamines be made available by prescription only, so as to discourage use by the general population.

It has been my clinical experience that many families still reach for Benadryl® (diphenhydramine) when their child is itchy, no matter the etiology. It is our responsibility, along with our pharmacy colleagues, to discourage the use of this outdated medication. CSACI strongly recommends that the "use of first-generation antihistamines should be significantly curtailed."[1]

Bleach baths

Another controversy in our day-to-day practice is whether or not to suggest bleach baths to our patients with recurrent *Staphylococcus aureus* infection. A recent systematic review found that bleach baths are effective in decreasing AD severity but are not more effective than water baths alone.[5] This study confirms that regular bathing is better than infrequent bathing in AD. A Cochrane review in 2010 found no benefits of using anti-staphylococcal interventions (i.e. bleach baths) to decrease the density of *S. aureus* on the skin of AD patients when compared to the regular use of anti-inflammatory medications we use to treat AD.[6]

In addition, a recent basic science publication looking at various laboratory models of *staph* eradication highlighted that the clinical concentration of dilute bleach baths we recommend to patients is actually not inhibitory to the survival or growth of *S.aureus* or *S.epidermidis*.[7] In reality, bactericidal effects were only seen at higher concentrations of bleach, levels that would be cytotoxic to human cells and could not be safely used in practice.

Dr Amy Paller, a prominent pediatric dermatologist in Chicago, has an interest in the microbiome and atopic dermatitis. In a recent study with Majewski et al, the investigators evaluated sodium hypochlorite (NaOCL) body wash in a 6-week, prospective, open label study which included 50 patients (ages 6 months to 17 years) with moderate-to-severe AD and proven *S. aureus* skin colonization. Patients were instructed to use the bleach-based body wash daily, in addition to their regular medicated creams. Primary endpoints included Investigator's Global Assessment (IGA), Eczema Area and Severity Index (EASI) and Body Surface Area (BSA) scores. At the end of the 6-week study, there was improvement in all outcome measures comparing baseline to 2-week and to 6-week evaluations. Interestingly, 64% of individuals were still positive for *S. aureus* at the conclusion of the study. The authors postulated that bleach baths and washes "involve a mechanism beyond its oxidative capability and bactericidal activity against *S. aureus*", suggesting that they may be anti-inflammatory without affecting bacterial dysbiosis.[8]

With all of this conflicting data, it is still difficult to know what to suggest to the patient and family sitting in front of you. The Canadian consensus statement on pediatric atopic dermatitis probably sums it up best: "bleach baths have not been consistently shown to improve outcomes in AD and may be used at the discretion of the treating health care provider."[9]

Early emollient use as primary prevention in atopic dermatitis

In 2014, Simpson et al published a paper which sent ripples of excitement throughout the dermatology world. A small pilot randomized controlled trial of 124 infants at high risk for AD looked at daily emollient use from <3 weeks to 6 months of age vs control and the subsequent development of AD. Parents in the intervention arm were instructed to apply full-body emollient therapy at least once-per-day starting within 3 weeks of birth. Parents in the control arm were asked to use no emollients. The primary clinical outcome was the cumulative incidence of atopic dermatitis at 6 months, as assessed by a trained investigator. At the conclusion of the study, regular emollient use showed a statistically significant protective effect on the cumulative incidence of AD with a relative risk reduction of 50% (relative risk, 0.50; 95% CI, 0.28-0.9; P = .017).[10] A similar small Japanese study showed another favourable result of 32% risk reduction of development of AD with daily emollient use.[11]

These findings spurred on the funding and recruitment of two larger cohort studies, one in the UK and one in Sweden.

The Barrier Enhancement for Eczema Prevention (BEEP) study was a multicenter, double-arm, parallel group randomized controlled trial recruiting patients from 16 sites across the UK[12], whose findings were recently published in *The Lancet*. In this study, 1394 infants with a high risk of developing AD were randomized 1:1 into application of petrolatum based emollients once a day in the first year of life vs standard skin care advice only (control). The primary outcome reported was development of AD at 2 years of age. The findings were somewhat surprising: 23% of children in the emollient group developed eczema vs 25% in the control group (adjusted relative risk 0.95 [95% CI 0.78 to 1.16], p=0·61; adjusted risk difference –1.2% [–5.9 to 3.6]) and 15% of

children in the emollient group had skin infections vs only 11% in the control group. The authors postulate the higher risk of infection may be due to increased inoculation of pathogens during emollient application, possible disturbance of the microbiome or possibly that emollients can make the skin more adhesive to bacteria. The authors concluded that there is no evidence to support daily emollient use in the prevention of AD in high risk infants, and that this might actually cause harm in the form of an increased risk of skin infections. "This practice should stop unless new evidence suggests otherwise".

In the same *Lancet* publication, the findings of the PreventADALL population-based study were also presented[13]. This study followed 2394 newborn infants for the first year of life, randomized into one of four groups: a control group (controls with no specific advice on skin care while advised to follow national guidelines on infant nutrition), a skin emollient group (bath additives and facial cream), a food intervention group (early complementary feeding of peanut, cow's milk, wheat, and egg), and a combined skin and food intervention group. The skin intervention consisted of the intervention 4 days a week, from age 2 weeks to 8 months of age. Even with this low level of intervention required, patients still had a low adherence to the full protocol. The primary outcome of AD at 12 months of age showed the highest rate of occurrence in the skin intervention group (11%) and the lowest rate in the combined skin and food intervention group (5%). This interesting and novel finding in the combined intervention group highlights the possibility that multiple interventions may work synergistically. This will hopefully be further elucidated when the extension of the study looks at allergy outcomes at age 3.

Taking these two large studies into consideration, there is no strong published evidence that daily use of an emollient in population-based or high-risk groups of infants in the first year of life can delay, suppress or prevent AD. These two studies used infrequent oil baths or daily petrolatum based products so it is possible that ceramide containing, low pH emollients may confer more of a benefit. The PEBBLES study is an ongoing large randomized controlled trial looking at similar outcomes but with a more sophisticated emollient used twice a day[14]. Even if this does show a positive outcome, it is unclear if a more costly cream and a more intensive regime would be a possible and realistic population-based strategy for reducing AD incidence.

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