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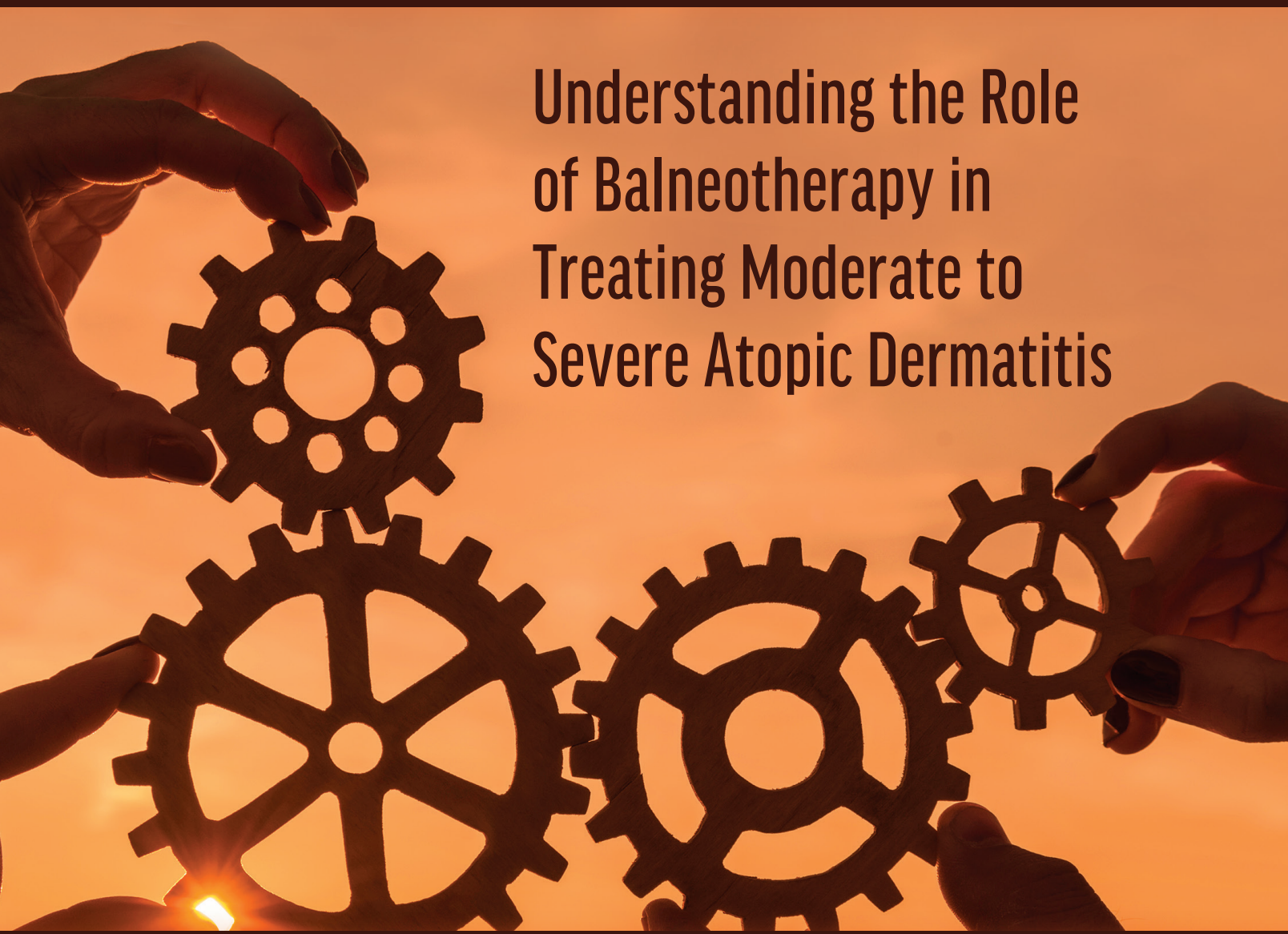
SETTING THINGS RIGHT

Understanding the Role of Balneotherapy in Treating Moderate to Severe Atopic Dermatitis



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SETTING THINGS RIGHT

Understanding the Role of Balneotherapy in Treating Moderate to Severe Atopic Dermatitis

Nights were the worst for Jason Lee-Llacer, MD, a critical care medicine specialist in Lanham, MD. And not because of his demanding job. His lack of ability to get a good night's sleep was instead due to the chronic itch associated with his severe atopic dermatitis (AD).

Dr. Lee-Llacer is not alone. According to the National Eczema Association (NEA), 31.6 million people in the US have some form of eczema.[1] The disease tends to begin in early childhood, but symptoms including vexing itch often remain throughout adulthood.

Dr. Lee-Llacer's condition worsened with age, and the relentless itch dramatically affected his sleep quality and overall quality of life throughout adulthood. At times, he would arrive at work with his head wrapped in Ace bandages because the eczematous lesions were oozing from all of his nighttime scratching.

"I was getting maybe an hour or two to sleep at night," he recalls. "It really affected me in terms of my performance of work." But that was then.

Now, thanks to a caring, attentive dermatologist, an effective medication regimen, daily maintenance treatment, and a two-week course of balneotherapy at the Thermal Care Center of La Roche-Posay in Central France, to help reset his skin's microbiome, Dr. Lee-Llacer has seen both his disease symptoms and quality of life—including sleep and itch—significantly improve.

Dr. Lee-Llacer is one of the fortunate ones. More than 55 percent of adults with moderate to severe AD report inadequate disease control, according to the NEA.[1] One in four adults with AD rate their health as "fair" or "poor." More than 16 percent are "very" or "somewhat" dissatisfied with life, and such negative ratings of health and life satisfaction increase with AD severity.

ITCH AS A BIOMARKER OF AD SEVERITY

A recent study of adults with moderate to severe AD found that 70.5 percent of adults reported severe, unbearable itch in the past two weeks, 85.8 percent reported daily itch, and 62.8 percent reported itching at least 12 hours per day.[2] Like Dr. Lee-Llacer, up to 30 percent of adults with AD experience issues including insomnia, daytime sleepiness and fatigue, and rate sleep disturbance as the "most" or "second-most" burdensome AD symptom.

"Itch…is a disease unto itself," says Dr. Lee-Llacer's dermatologist, Adam Friedman, MD, FAAD, Professor and Interim Chair of Dermatology, Residency Program Director, Director of Translational Research, and Director of the Supportive Oncodermatology Program in the Department of Dermatology at The George Washington University School of Medicine & Health Sciences in Washington, DC. "Certainly, there could be itch with no rash, but the itch of atopic dermatitis is somewhat unique in that it feels so unbelievably good to scratch. There's this positive feedback."

He continued, "You scratch more, you create more inflammation, create more itch, you go on and on and on and on. We know [itch] is a good biomarker for treatment success, but also we know this is what's going to drive people nuts."

AD IS A FAMILY AFFAIR

It's not just the individual with AD that is affected by the condition. Dr. Lee-Llacer's nights were so bad that his wife, Agnes Abeleda, RN, had to give up her job as a critical care nurse. "What I did at night to prevent him from scratching was massage his body, because then his mind would be off

Impact of AD on Adults

- 70.5%: Severe, unbearable itch in the past 2 weeks
- 85.8%: Daily itch
- 62.8%: Itching ≥12 hours/day
- ~30%: Insomnia, daytime sleepiness and fatigue

"You need a long-term plan. Our goal is about preventing repeated flares and preventing this disease from being extremely disabling and impacting every facet of quality of life."

the scratching and just the pressure and the stimulus was greater than the itch for him," Ms. Abeleda says. As a result, she began sleeping during the day. The couple says they were concerned that Dr. Lee-Llacer's ongoing lack of sleep could begin to impair his job performance. Ms. Abeleda put her career on hold to ensure he could get healthy and be performing at top ability for his critical care patients.

"Chronic inflammatory diseases aren't just affecting that one person, they're affecting the whole family network as well," confirms Dr. Friedman.

Dr. Lee-Llacer and Ms. Abeleda shared their experiences at the 2020 ODAC Dermatology, Aesthetic and Surgical Conference (with Dr. Friedman) and at the 2020 Fall Clinical Dermatology Conference (with Neal Bhatia, MD).

SHARPENING THE GOALS OF AD THERAPY: THE YARDSTICK APPROACH

The goals of AD therapy are multi-faceted. They include preventing complications, controlling symptoms such as itch, reducing the extent and severity of the disease, clearing skin lesions, preventing relapses and flares, and maintaining remission and improving quality of life.

"You need a long-term plan, because our goal is not to treat just that flare right then and there," Dr. Friedman says. "Our goal is about preventing repeated flares and preventing this disease from being extremely disabling and impacting every facet of quality of life."

The treatment process starts with making sure that you have the correct diagnosis. Looks can be deceiving, Dr. Friedman says. Other conditions may look like or mimic eczema, including dermatophytosis, cutaneous T-cell lymphoma, drug reactions, and even blistering diseases.

Once a clear AD diagnosis is established, the discussion turns to treatment and maintenance therapy. "You have to optimize an active treatment, but also maintenance therapy using things like soap education, detergent education and appropriate moisturizer use," Dr. Friedman says. "It is really important to think about all these things." All atopic patients must keep their skin moisturized regardless of the activity, severity of their disease or current treatment regimen.

Simply treating flares as they occur is not an effective AD management strategy. "If you take the approach that I'm going to treat it as it comes, not only will you not get good control, but it really facilitates a lot of the comorbidities that we see emerging," says Dr. Friedman.

More than 20 percent of adults with AD also have asthma; their risk for allergic rhinitis and food allergy is two to four times higher; and they are at increased risk of developing serious bacterial, viral and fungal skin infections, the NEA points out.[3] Moreover, AD in adults is associated with diabetes, obesity, autoimmune disease, high blood pressure and heart disease, and the risks for these conditions increases with AD severity. Adults with AD also have a two-and-a-half to three-fold higher risk for anxiety or depression that increases with disease severity.

Currently Dr. Lee-Llacer takes methotrexate and cyclosporin along with bi-weekly shots of dupilumab to control his AD. "I try to use steroids sparingly because I don't want to use a ton of steroids and cause more atrophy on my skin," he says. He also applies pimecrolimus, 1%, to his face. "I shower at night and I'll apply some oils just so that when I'm going out of the shower after I dry off with a towel, I'm not super dry," he says.

THE ROLE OF BALNEOTHERAPY IN AD MANAGEMENT

Breaking the cycle is where balneotherapy may play a role, Dr. Friedman says. Dr. Lee-Llacer spent two weeks at the Thermal Care Center of La Roche-Posay in Central France, a thermal water treatment center dedicated to dermatology, as part of his overall AD treatment regimen. Here, treatments including high-pressure filiform showers, baths, facial and body spray treatments, as well as La Roche-Posay thermal water consumption, take place

Common AD Mimickers

Psoriasis

Seborrheic dermatitis

Infectious skin diseases

Genetic skin disorders

"Adults with AD also have a two-and-a-half to three-fold higher risk for anxiety or depression that increases with disease severity."

Monday through Saturday at the facility. Led by eight dermatologists, the Center welcomes 7,500 patients every year, up to 30 percent of whom are children.

Dr. Lee-Llacer is one of more than 400,000 patients who have been treated at the Center since 1905. Patients treated at the Center are asked to come back usually once a year, and most stay for three weeks per session. The precise regimen consists of an 18-day treatment with a daily high-pressure filiform shower (15 bars for three minutes) using crude thermal spring water.

"It's not really a spa as you would think of these dermatological spas, it's more like being in a gym," Dr. Lee-Llacer recalls. "Basically you line up, you see your dermatologist and they prescribe you their medication or their treatment regimens."

Dr. Lee-Llacer still moisturizes with a bespoke product made for him at the Center. "I use that since I have a couple of tubes left, which expire this month. I'm trying to use that all up," he says.

To fully understand the potential benefits of balneotherapy as part of an overall AD management plan, it's important to understand the causes of this chronic inflammatory disease, Dr. Friedman says.

AD results from a complex interaction between genetics and the environment, and both decreased skin barrier function and complex immune dysregulation play a role. Barrier dysfunction may be more significant in adult AD than in pediatric disease. "Inflammation that is aberrant and out of control in and of itself can disrupt the skin barrier and inhibit the development of ceramides and lead to defects in filagrin formation and crosslinking." Dr. Friedman notes.

Balneotherapy is thought to work in part by restoring balance of the skin's microbiome, he explains. "The microbiome is the genetic makeup of the organisms on our skin; the microbiota are those actual organisms," he says. "We have more than 500 species that we know of that live on our skin, and when all the right players and the right amounts are where they're supposed to be, everyone is happy. They protect us from the outside world.

When our skin's microbiota gets disrupted, however, things go wrong and dysbiosis occurs, Dr. Friedman says.

AD is the poster child for dysbiosis, he continues. "If we even look at unaffected skin of patients with AD, we do see inherent differences in the populations that live on the skin compared to the skin of people who do not have AD," he says. Of note, *Staphylococcus* is more present in affected skin than unaffected skin in AD, but there is an abundance of firmicutes on affected and unaffected skin in a patient with AD. What's more, nonlesional skin also harbors other AD-specific inflammatory changes.

Impact of AD on Adults

20%: Adults with AD who also have asthma

2-4x: Increased risk for allergic rhinitis, food allergy

\+ Increased risk for serious bacterial, viral, fungal skin infections

2.5-3x: Risk for anxiety or depression

AD in adults is associated with diabetes, obesity, autoimmune disease, high blood pressure, and heart disease

"Treating AD is a marathon, not a sprint."

STRIVING FOR DIVERSITY

Healthy skin is microbial diverse skin. "Maintaining a diverse microbiota is central to ensuring a stable barrier but also may be limiting activity of chronic inflammatory diseases," Dr. Friedman says.

In fact, a decrease in diversity happens even before a clinical flare of AD. "When you treat atopic dermatitis with topical steroids and emollients, patients go back to their original baseline from non-lesional skin, so it's very telling that we really need to respect the microbiota and facilitate and help them grow."

Dr. Lee-Llacer's Eczema Voyage

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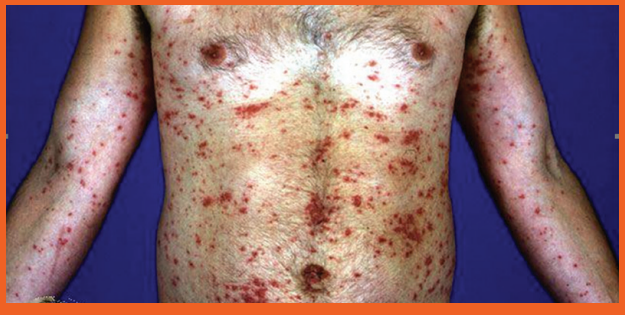
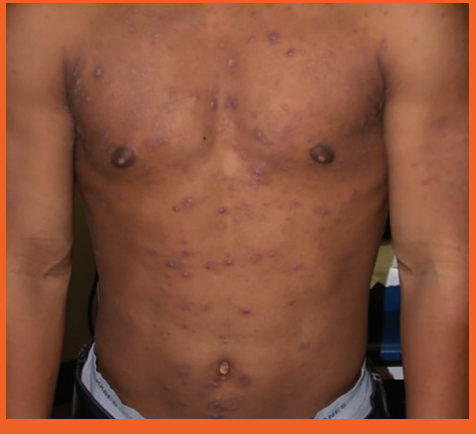


Dr. Lee-Llacer's eczema worsened with age, leading him to attempt multiple prescription drugs.

2



Itch dramatically affected sleep and overall QoL.

3

Agnes Abeleda, RN, Dr. Lee-Llacer's wife, gave up her job as a critical care nurse to assist him through the night and she slept through the day.

4

Dr. Lee-Llacer begins a new medication regimen and attends a two-week course of balneotherapy at the Thermal Care Center of La Roche-Posay in Central France.

5

Dr. Lee-Llacer has seen both his disease symptoms and quality of life—including sleep and itch—significantly improve.

6

Currently Dr. Lee-Llacer takes methotrexate, cyclosporin and bi-weekly shots of dupilumab to control his AD. His supportive OTC skincare regimen includes La Roche-Posay Lipkar Balm AP+ Moisturizing Cream.

"Thermal spring water has been used for medicinal purposes since Roman times. In addition to other minerals and other non-pathogenic microbes, La Roche-Posay thermal spring water (LRP-TSW) at the thermal center is rich in selenium, which has been shown in clinical studies to provide many benefits and helps build and maintain a diverse, protective skin microbiome."

SELENIUM, SPRING WATER, AND MICROBIOTA DIVERSITY

Thermal spring water has been used for medicinal purposes since Roman times. In addition to other minerals and other non-pathogenic microbes, La Roche-Posay thermal spring water (LRP-TSW) at the thermal center is rich in selenium,which has been shown in clinical studies to provide many benefits and helps build and maintain a diverse, protective skin microbiome. "Selenium is actually used in various over-the-counter cosmeceuticals because of its antioxidant properties," Dr. Friedman says. The water is used as a key ingredient in most La Roche-Posay skincare formulas, along with other ingredients to provide a variety of benefits.

Selenium can facilitate the growth of certain organisms including gram-negative bacteria of Xanthomonas genus. "Gram negatives get a bad rap, as we think about pathogens like *Pseudomonas* and *E. coli*, but actually gram negatives are quite good," Dr. Friedman says. "While they make up a very small amount or percentage of that overall population on the skin, they actually account for about 50 percent of the microbial diversity."

When *Xanthomonas* go up, we tend to see Staph goes down, and that's a very good thing, he says. Specifically, "when Staph decreases, diversity increases, and flares end."

This is the essence of probiotic and prebiotic therapy. The LRP Thermal Spring Water at the Thermal Care Center contains live microorganisms and as such can be considered probiotic and therefore may play a contributing factor in support the growth of these regulatory microrganisms on skin. "If we intervene with something that will facilitate the proper organization in those microbial communities, we could potentially stop an additional flare," Dr. Friedman says.[3]

Balneotherapy is not just a matter of restoring the balance of the skin's microbiome, he says, noting that the organisms need strategic support in order to thrive and maintain their share of the community. "We are giving the support to become stable. We're giving them the things to survive."

When researchers sampled skin microbiota on one eczema lesion and one adjacent unaffected skin site on 35 AD patients to analyze microbiota diversity (Shannon diversity index), bacterial phyla and genus abundance as well as the severity of AD with SCORAD before and after three weeks

of balneotherapy, the SCORAD improved from 54 ± 16 to 23 ± 10 (-56% in average) at the end of the balneotherapy period.[4]

At the bacterial level, before balneotherapy, the Shannon index was lower on the affected skin compared to the adjacent unaffected skin, but the Shannon index increased after balneotherapy and became similar on both areas. Moreover, after balneotherapy, the abundance of firmicutes was reduced in both areas, and other phyla increased. The decrease of firmicutes was due to a significant reduction of *Staphylococci* in both areas, the study found. Lastly, an increase in the amount of *Xanthomonas* genus was also observed. Patients presenting with atopic dermatitis are significantly improved at the end of a three-week balneotherapy at La Roche-Posay Thermal Care Center, the researchers concluded. These findings are similar to what has been seen in psoriasis patients treated with balneotherapy at the Center.

A review of several studies found that prebiotics and selenium-rich thermal spring water also increases the efficacy of moisturizers and that some of this benefit may be due to positive effects on skin microbiota.[5]

An emollient containing a high concentration of LRP-TSW and other key ingredients or the use of LRP-TSW alone during balneotherapy reduced disease severity and increased the diversity of skin microbiota in patients with either AD or psoriasis, the study showed. In both groups of patients, there was an increase in keratolytic bacteria of the *Xanthomonadaceae* family that are naturally present at low levels on the skin and in LRP-TSW.[3]

AVOIDING AD TRIGGERS

Part of AD treatment also involves avoiding any triggers. "AD is very protean in its manifestations," says Dr. Friedman. "Simple differences from patient to patient can play a huge role in terms of how it manifests. This can include skin prototype, comorbidities and environment," he says. "A patient with atopic dermatitis in Arizona is going to look very different than a patient with atopic dermatitis in New York City because environment, nature, and nurture play a very big role in managing this condition."

Heat is a very big trigger for Dr. Lee-Llacer. "If my body temperature gets up, I'm going to start flaring and I'll get this almost histamine-type reaction. I'll feel the warmth, I'll feel itchy."

REDEFINING TREATMENT SUCCESS AND FAILURE

There is no approved biomarker to predict treatment response yet, and there is not universal agreement on a standardized definition for treatment failure in AD, Dr. Friedman says. Some parameters include inadequate clinical improvements, failure to achieve stable long-term disease control, and/or the presence of ongoing impairment, pruritus, pain, or loss of sleep.

Given this uncertainty, managing patient expectations throughout treatment is essential, Dr. Friedman says. Part of this involves optimizing your relationship with the patient. "Anytime I have a new atopic patient come in, I see them back in three to four weeks," he says. "Establishing that relationship early on is so important because these are lifelong patients. Treating AD is a marathon, not a sprint." ■

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