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From Symptom Control to Targeted Treatment: The Shifting Paradigm of Atopic Dermatitis

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From Symptom Control to Targeted Treatment: The Shifting Paradigm of Atopic Dermatitis

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable discussion held in April 2017.

TARGET AUDIENCE

This certified CME activity is designed for dermatologists, dermatology nurse practitioners and dermatology physician assistants involved in the management of atopic dermatitis.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Identify the mechanisms of action, efficacy, and safety of emerging targeted therapies for AD
- Recognize the lifestyle measures and daily skin care practices that are the foundation of AD treatment plan
- Discuss the prevalence, presentation, and quality-of-life effects of AD in adults
- Interpret and explain the recognized and emerging comorbidities associated with AD in children, adolescents, and adults

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From Symptom Control to Targeted Treatment: The Shifting Paradigm of Atopic Dermatitis

Is this the decade of atopic dermatitis (AD)? After more than 15 years without a new drug for this potentially devastating cutaneous disease, we now have two new therapeutic options and many more drugs in development. Research on the factors that contribute to the pathogenesis AD is flourishing.

A panel of leading experts convened to discuss the current treatment of AD, with an emphasis on new and emerging therapies. The objective is to review the new treatment landscape for AD within a practical clinical framework that translates new drugs and research into meaningful patient care.

Peter A. Lio, MD: This is an amazing time to be interested in atopic dermatitis (AD). The disease has been in the shadows for a while, but recently there have been significant advances and innovations.

Let's begin by talking about the immunopathogenesis of AD. When reviewing the history of theories about the pathogenesis of this disease, I find it interesting that we have gone from an immune theory, to a period when the skin barrier function was thought to be predominant, and now we are moving back to an immunocentric theory of the disease. Of course, we now have targeted therapies, so we have diagnosis "ex juvantibus"—the idea that if a drug improves a disease then the drug's mechanism of action must be critically important, if not the main driver of the disease.

Robert Sidbury, MD: I think you captured it well; we've come almost full circle. It's fascinating that we can treat AD both with emollients and other agents that work on the outside of the skin and with powerful immunosuppressants such as cyclosporine that offer benefit without clearly affecting the skin barrier.

We have two paradigms of AD: outside-in and inside-out. [1-4] We're marrying both paradigms with some of the newer data—both the scientific data about therapeutic targets and genetic data focusing on genes like filaggrin.

David Fivenson, MD: I like to think of the outside-in/inside-out paradigms of AD in terms of yin/yang—you can't have one without the other. Factoring in both sides of the equation gives us more direction in how we choose therapy. It also helps us explain the disease to patients and the lay public, because on the face of it many patients find it crazy that we can treat AD by rubbing on some moisturizer or by using targeted, high-powered immunosuppressive therapy. Both sides of the equation elucidate the disease and help us educate patients.

Dr. Lio: The multifactorial aspects of AD produce multipronged approaches to treatment. One of my favorite papers from a few years ago showed that even in patients who make normal filaggrin, inflammatory cytokines decreased filaggrin expression, so patients became functionally deficient in filaggrin.[5] And that's only one piece of the puzzle. There are beautiful studies showing that psychological stress and sleep deprivation can functionally damage the skin barrier.[6-8]

It's interesting to see AD as a holistic process—the mind, the body, the immune system, the skin, all coming together, all playing off each other. You can target one aspect and produce effects throughout the whole system. You can rebalance.

NOVEL TARGETED THERAPIES FOR ATOPIC DERMATITIS

Dr. Lio: Dupilumab was approved by the US Food and Drug Administration (FDA) and launched in March 2017.[9] The drug's indication is for the treatment of adults with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. It is administered by subcutaneous injection and can be used with or without topical corticosteroids.

Dupilumab is a fully human monoclonal antibody directed against the shared alpha subunit of the interleukin-4 (IL-4) receptors that blocks signaling from both IL-4 and IL-13.[10] It's not an immunosuppressant. It's almost as if we've begun the era of biologics for the treatment of AD with a third-generation biologic.

What are your thoughts about dupilumab in terms of the mechanism of action? Is this drug going to work for everyone, or will there be subgroups in which it is more efficacious? Do we think efficacy in the clinic will be as good as it looks in the phase 3 clinical trials? (Table 1) And what about safety?

Dr. Sidbury: We've come a long way from medications that non-

TABLE 1. EFFICACY OF DUPILUMAB IN TWO PHASE 3 TRIALS

	Solo 1			Solo 2		
	Dupilumab (Weekly)	Dupilumab (Every Other Week)	Placebo	Dupilumab (Weekly)	Dupilumab (Every Other Week)	Placebo
	N=223	N=224	N=224	N=239	N=233	N=236
IGA score = 0 or 1, plus 2-grade or greater improvement from baseline	37%	38%	10%	36%	36%	8%
(Week 16)*	(p<0.001 vs placebo)	(p<0.001 vs placebo)		(p<0.001 vs placebo)	(p<0.001 vs placebo)	
EASI-75	52%	51%	15%	48%	44%	12%
(Week 16)	(p<0.001 vs placebo)	(p<0.001 vs placebo)		(p<0.001 vs placebo)	(p<0.001 vs placebo)	
≥3 points improvement in peak score for pruritus	52%	47%	17%	49%	51%	13%
(Week 16)	(p<0.001 vs placebo)	(p<0.001 vs placebo)		(p<0.001 vs placebo)	(p<0.001 vs placebo)	

* Primary end point
IGA = Investigator's Global Assessment
EASI-75: Improvement from baseline of at least 75% on the Eczema Area and Severity Index
Simpson EL, et al. N Engl J Med. 2016; 375:2335-2348.[10]

specifically suppress an immune response. Of course, we have immune responses for a reason: They help us stay healthy and fight infection. If you use cyclosporine or other immunosuppressants that are nonspecific, you'll get not only the potential benefit but a much greater risk for adverse effects.

When you transition to a drug that's much more specific, like dupilumab, and you're targeting a specific molecule, you might logically expect a cleaner side-effect profile. We have interesting phase 3 data published on adults[10] and open-label, phase 2 data in children were presented at the 2017 Annual Meeting of the American Academy of Dermatology.[11] In the adult trials, other than injection site reactions, conjunctivitis was the most frequent treatment-related adverse event.[10] It will take time for us to learn more and see what the data mean in a larger population, but, as you say, the more targeted the approach the better.

Mark Lebwohl, MD: You said that dupilumab is not immunosuppressive, and I assume that what you mean is that we're not seeing opportunistic infections, and that's certainly true. This drug does target IL-4 and IL-13, which certainly play a role in the immune system, but blocking these cytokines doesn't seem to predispose to opportunistic infections. As we stated earlier, the most frequent side effect, interestingly only in AD and not asthma, was conjunctivitis.[10,12]

Dr. Fivenson: I'm excited about dupilumab. The data, especially in combination with topical steroids, is impressive. I wrote two prescriptions for it today, both for patients who had been on mycophenolate mofetil for about one year. That is the patient scenario in which I think we will get the most comfort and utility from this drug—getting patients off more broad-spectrum immunosuppressants.

I do think we need to at least think about some of the other Th2-mediated processes that are somewhat suppressed by blocking IL-4 and IL-13, such as cutaneous T-cell lymphoma and certain parasite infections. These are some of the outliers that we might keep our eyes open for.

Dr. Lio: Crisaborole, the other new treatment, was approved in

TABLE 2. EFFICACY OF CRISABOROLE IN TWO PHASE 3 TRIALS

	Study 301		Study 302	
	Crisaborole	Vehicle	Crisaborole	Vehicle
	N=503 (ITT)	N=256 (ITT)	N=513 (ITT)	N=250 (ITT)
ISGA score = 0 or 1, plus 2-grade or greater improvement from baseline (Day 29)*	32.80% (p=0.038 vs vehicle)	25.40%	31.40% (p<0.001 vs. vehicle)	18.00%
ISGA score = 0 or 1 (Day 29)	51.70% (p=0.005 vs. vehicle)	40.60%	48.50% (p<0.001 vs. vehicle)	29.70%

* Primary end point
ISGA = Investigator's Static Global Assessment
Paller AS, et al. J Am Acad Dermatol. 2016; 75: 494-503.[14]

December 2016.[13] It is a topical phosphodiesterase 4 (PDE4) inhibitor in an ointment base indicated for the treatment of mild-to-moderate AD in patients two years of age and older.

It's an important innovation because it is not a corticosteroid and it is not a calcineurin inhibitor. Unfortunately, the boxed warning on the calcineurin inhibitors made these drugs more difficult to prescribe, even though I think most of us are confident that they are quite safe when used appropriately and that the malignancy risk described in the boxed warning is theoretical.

I'm excited about crisaborole because it has a new mechanism of action, it's nonsteroidal, it doesn't have a boxed warning, and it is FDA approved as a first-line treatment down to the age of two. (Table 2)

Dr. Fivenson: For specific body regions that are very sensitive and highly susceptible to corticosteroid toxicity, such as the face, neck, inner thighs, and behind the ears, crisaborole will be a useful drug. I've also begun to see more patients, especially those with acute disease, who don't want to use topical calcineurin inhibitors because of stinging and burning, and crisaborole might be useful in these patients. I'm also excited that this drug may have utility in some of the connective tissue diseases, such as lupus erythematosus and dermatomyositis, especially in sensitive body regions.

Dr. Lebwohl: Crisaborole fills the niche that topical calcineurin inhibitors filled simply because they are not steroids, so you can use them in places like the face or groin or areas where you want to avoid skin atrophy and striae. The difference between crisaborole and the calcineurin inhibitors is that crisaborole doesn't carry a boxed warning. Crisaborole appears to have an excellent safety profile. The only adverse reaction that occurred in ≥1% of patients treated with crisaborole in clinical trials was application site pain (stinging or burning), which occurred in 4 percent of patients.[14] Contact urticaria was a less common adverse reaction. We also have the example of apremilast, which is another PDE4 inhibitor, although it is an oral drug indicated for the treatment of psoriasis.[15] Apremilast is certainly quite safe. We can use crisaborole in body areas where we can't use triamcinolone and other corticosteroids, especially long-term.

Dr. Sidbury: I agree with everything Dr. Lebwohl and Dr. Fivenson said. I'd also like to offer some historical perspective. I was a resident with Jon Hanifin in 1993 when he and Sai Chan published a paper showing that atopic monocytes had abnormal phosphodiesterase activity.[16] And here we are in 2017 finally having a drug resulting from that scientific advance. It gives us some insight and perspective on how long the journey is from bench to bedside.

It is interesting that in the phase 3 studies of crisaborole, almost one out of three patients in the treatment group reached "clear or almost clear" vs one out of four in the vehicle group. This tells us about the patient population in the studies—the patients had relatively mild AD. But it also tells us a bit about how good vehicles are these days.

"As we all know, the best moisturizer in the world won't help if it sits on the shelf. We want to make sure that parents and patients realize that the thicker the better—all other things being equal. I want a moisturizer to have relatively few preservatives, no fragrances, and I want a moisturizer that the patient will use often, especially after a bath."

—Dr. Sidbury

The patient population I anticipate treating with crisaborole are those who are frightened of current options: patients and parents with steroid phobia and boxed-warning phobia. Finally, I would circle back to what you said earlier, Dr. Lio. Any advance in AD that is FDA approved down to the age of two is an advance we should welcome.

Dr. Lio: Let's discuss some other potential therapies.

Ustekinumab has been used off-label in some cases of severe AD,[17-20] and apremilast is in phase 2 trials for AD.[21,22] A phase 2b dose-ranging and efficacy study of tralokinumab, a monoclonal antibody that targets IL-13, has been completed in adults with moderate-to-severe AD.[23] Lebrikizumab, another IL-13 blocker, is also being investigated.[24]

I'm interested in the Janus kinase (JAK) inhibitors, especially tofacitinib, which is an oral drug approved for the treatment of moderate-to-severe rheumatoid arthritis. A paper from Yale University reported the successful tofacitinib treatment of six patients with moderate-to-severe AD who had failed standard treatments. [25]

What do you think of these other medications? What roles might they play and where does this lead us in terms of immunopathogenesis?

Dr. Lebwohl: JAK inhibitors are broadly immunosuppressive, unlike dupilumab. The holy grail would be a small molecule medication like a JAK inhibitor that does not have a high frequency of immunosuppression-related side effects. If you look at the studies, I think the FDA did not approve tofacitinib for psoriasis because we have many other drugs available for psoriasis that are targeted and

less immunosuppressive.[26] Also, there were a fair number of cases of herpes zoster and some lymphomas in patients treated with tofacitinib. So I think the FDA was appropriately cautious. I will say that tofacitinib may get approval for other conditions for which we don't have good treatments, such as vitiligo or alopecia areata, and perhaps even AD.

There are other classes of oral agents that might play a major role in AD. Apremilast, for example, is modestly effective in psoriasis but many patients are taking it because they are willing to take a pill but not willing to take an injection.[15]

Dr. Sidbury: I've been excited about these other molecules as well. Dr. Lio, you described treatment with an oral JAK inhibitor, but topical JAK inhibitors are being studied in AD as well.[27] A topical formulation of a JAK inhibitor might be another way to see benefit without the potential adverse effects Dr. Lebwohl characterized.

A phase 2 trial of the IL-31 blocker nemolizumab in the treatment of AD was just published;[28] IL-31 is often referred to as the "itch cytokine."[29] Itch, of course is the sine qua non of AD, and targeting itch would be another holy grail of therapy. If you have a treatment for AD that doesn't address the itch, it's not a treatment for AD. That's why this drug in particular excites me.

Dr. Lio: That's a great point. I love the idea that if we could target the itch, maybe we wouldn't need to be as broadly immunosuppressive.

Dr. Fivenson: I want to throw out a pitch for some of the data on leflunomide, because it has many of the effects of some of the newer, more targeted agents besides inhibiting DNA synthesis at the mitochondrial level.[30-31] It's a JAK inhibitor, it decreases IL-4 and IL-13 production independently, and has antibacterial effects, all of which are some of the components of some of the more targeted AD therapies. It's a relatively safe molecule for long-term use. I think it could at least be a prototype for repurposing some of the older medications.

Dr. Lio: I've not heard much about leflunomide for AD. But I think it's a great point, and it would be interesting to see if it makes a comeback now that we're using some of these more powerful medications, or if a cousin of leflunomide is developed specifically for AD.

I'd like to discuss the role of *Staphylococcus aureus* and the microbiome. I remember a paper that talked about making a healthy probiotic soup and applying it to the skin of patients with AD to decrease *S aureus* and eczema severity.[32] We just completed a very small trial looking at a topical probiotic spray.

I think we're seeing more and more that *S aureus* is not just an innocent bystander, it's not just a colonizer; it plays an active role in encouraging the inflammatory response by acting as a superantigen stimulating T cells. A paper came out in 2013 that described how *S aureus* produces the delta toxin, which is directly damaging to the skin barrier.[33] So I think there is a new level of focus on bacterial balance.

Dr. Sidbury: This discussion dovetails with the paper Richard Gallo's laboratory just published looking at the cutaneous microbiome as a whole.[34] They elegantly showed that coagulase-negative Staphylococcus (CoNS) strains produce antimicrobial peptides, and when you look at atopic skin, those CoNS that produce antimicrobial peptides are either diminished or absent. Ergo, you get *S aureus* colonization. If you reintroduce those CoNS strains to atopic skin, *S aureus* colonization is diminished.

So it does seem as though there is cutaneous dysbiosis that promotes *S aureus* colonization that then can act as a superantigen and exacerbate the dermatitis. We need look no further than the role of bleach baths in not only reducing the risk of infection but improving AD everywhere but above the neck, where kids aren't sitting in water. It's a fascinating story.

Dr. Fivenson: I'm still fascinated by the simple finding that changing the skin pH can selectively change how Staphylococcus responds on atopic skin vs unaffected skin.[35] Some currently available over-the-counter moisturizers as well as some of the newer anti-itch preparations containing hypochlorous acid can significantly change the colony counts of Staphylococcus with very inexpensive therapy.[36]

Dr. Lio: There are so many pieces to the puzzle: pH, probiotics, synbiotics (a mixture of prebiotics and probiotics).[37] This is going to be an important area to watch.

NON-PHARMACOLOGIC MANAGEMENT OF ATOPIC DERMATITIS

Dr. Lio: Dr. Fivenson, your comment is a perfect segue to a discussion of the nonpharmacologic management of AD. Let's begin by thinking about moisturization and the barrier function. Today we have an embarrassment of riches of moisturizers as well as barrier repair creams. I know that some clinicians are skeptical about barrier repair creams. I think they're probably overpriced for what they do, but I am grateful for their existence because occasionally I have a patient who seems to respond well or really likes them.

How do you select moisturizers for your patients? Do you think one size fits all or do you look at the phenotype and make a judgment?

Dr. Sidbury: Moisturization and bathing are foundations of AD care, and, true to the vexing nature of the disorder, there is a lot of misinformation and confusion.

If we focus on your more granular question about the role of smarter emollients, as we call them, with ceramides and other ingredients, I don't use them a lot. However, I think they're an advance, and there are patients for whom they are helpful. But we have plenty of patients who still have challenges finding a moisturizer

that works for them.

In every comparative study I've seen that looked at smarter moisturizers versus dumb old petrolatum, petrolatum tends to come out looking pretty good.[38,39] But as we all know, the best moisturizer in the world won't help if it sits on the shelf. We want to make sure that parents and patients realize that the thicker the better—all other things being equal. I want a moisturizer to have relatively few preservatives, no fragrances, and I want a moisturizer that the patient will use often, especially after a bath.

Dr. Lio: That's my exact approach. I give patients several samples or even bring in testers during the appointment and let patients try them, "Try this. How do you like this one?" If you give a patient a product they really like in the clinic, I think they're more likely to use it. But I don't have a specific moisturizer for everyone; I let them explore a bit, as long as the moisturizer meets our basic criteria.

Dr. Fivenson: I'm a bit more in favor of the barrier repair agents, and I've recommended them more often as they've become more affordable. I think that convincing parents of the importance of moisturization is crucial, especially since there are good data showing that the application of a moisturizer to neonates in eczema-prone families prevents the development of AD.[40,41]

I have a long list of lotions, creams, and ointments that I hand out about 20 times a day and update periodically. I note my favorites with asterisks, and include basic information about how to care for dry skin.

Dr. Lebwohl: The same moisturizer does not work for everybody, so I individualize my recommendations depending on what the patient tells me. There are some patients who complain that they itch more if they apply a greasy ointment like petrolatum. There are others who do better with a greasy ointment. So I ask patients what they prefer. If lesions are impetiginized, I am more likely to incorporate bleach baths. If a patient complains that everything they put on their skin stings, I recommend moisturizers that contain dimethicone because it is a protective ingredient and moisturizers that contain dimethicone tend not to sting. I've noticed this in practice, and we also published a paper on sunscreens, which demonstrated that sunscreens containing dimethicone were less irritating for patients with sensitive skin.[42]

If patients itch a lot, there is a role for menthol. Some topical antipruritics and moisturizers contain menthol, which might be beneficial.

When we began this discussion, you asked if there is a phenotype of patients that tells us to go in one direction versus another. Emma Guttman-Yassky, who is in my department, has looked at the cytokine profiles of different groups of patients, and there do appear to be differences.[43] For example, Asians with AD have more of an IL-17/IL-23 cytokine profile, which you would expect in lichenified AD lesions that are thick like psoriasis lesions. In comparison, white patients have less of an IL-17/IL-23 profile. So the day may come when we may be able to characterize patients, either phenotypically or genetically, and recommend the treatment that will work best for them, but we're not there yet.

"For the majority of patients, especially adults, diet plays very little role in AD. I will qualify that observation by saying that if a patient knows of a food that makes their AD worse, then obviously they should stay away from that food. But I think in most cases diet plays a very small role. So I try to get patients to focus on care of the skin."

—Dr. Lebwohl

Dr. Sidbury: I agree with everything Dr. Lebwohl and Dr. Fivenson said. And I would add that when we think about petrolatum versus the barrier creams and the relatively cheap versus the relatively expensive, a paper was recently published that looked at cost effectiveness of moisturizers for AD by examining quality-adjusted life-years, and even the most expensive emollient was cost-effective.[44] And those findings don't even take into account what Dr. Fivinson was getting at in terms of potential primary prevention of AD and other comorbidities. So I think it's important to remember how effective moisturizers are when the rubber meets the road.

Dr. Lio: The cost-savings associated with moisturization is staggering.

Let's move on to bathing and the selection of cleansers. Some studies have been published recently, but it's a difficult topic.[45,46] Everyone seems to have strong opinions about bathing frequency, but when you go to the primary literature, you realize that there is not a lot to guide us.

What do you think about the bathing and cleansing situation?

Dr. Sidbury: It is a situation! On the guidelines committee, most of us were of the "soak and smear" school [daily bathing followed by immediate smearing of a topical steroid ointment during intensive therapy and an emollient during maintenance therapy].[47-48] Then we looked at the evidence, especially Larry Eichenfield's study. In this study, five children age 11 to 16 years with mild-to-moderate AD and five subjects age 8 to 30 years with unaffected skin received

four bathing/moisturizing regimens: bathing without emollient application; bathing and immediate emollient application; bathing and delayed emollient application; and emollient application alone.[49] Emollient application alone achieved significantly greater skin hydration compared with the other regimens.

I think the lesson is to not be dogmatic about bathing with parents and patients. AD is an individual disease. There are general principles, there are guiding points that are bedrock truth, but at the same time all patients have their own twist on it, so I tell parents that they are the experts on their child's skin. As long as people keep irritating soaps and other products out of the bath and as long as they moisturize immediately afterwards, it's up to them to decide if it's best to bathe once a day or once a week.

Dr. Lebwohl: The "soak and smear" dogma is so strong that some people just don't believe there is a downside to bathing, but the Eichenfield paper proved that the dogma is wrong.

I ask the average patient whose skin is not impetiginized to minimize the use of soap and water. I give out an instruction sheet that recommends showers, not baths—not too hot, not too long, quick in and out—and immediate application of medication or moisturizer. People who bathe twice a day are doing themselves a disservice. If the patient's skin is impetiginized, I modify the recommendation because I think those patients benefit from soaking, especially in bleach baths.

Dr. Lio: Another issue in the nonpharmacologic management of AD is the avoidance of environmental triggers. We touched on this when we discussed avoiding harsh detergents, certain preservatives, and fragrances in moisturizers and cleansers. It is recommended that patients avoid recognized mechanical and chemical irritants, such as wool and solvents, as well as individual triggers such as excessive heat. But I don't spend a lot of time on other environmental triggers. Actually, I spend time redirecting patients away from worrying about food allergies—except in cases of specific, known food allergies, of course. I hear a lot of questions about tomatoes, gluten, dairy, and dust mites. I've actually been reprimanded. At the end of a long visit sometimes a patient will say, "You didn't even tell me what to avoid in terms of grasses and molds and dust mites."

What are your approaches?

Dr. Sidbury: I have a similar approach. I see only children, so that's a bias. First, if I dismiss the possibility of allergy as a cause, oftentimes the parents will dismiss me. I try to redirect them, encourage them to focus on skin care first, especially if the child has mild-to-moderate AD. Actually, I encourage them to focus on skin care first, second, and third. I emphasize the principles we've been talking about. Unless there is a compelling history—because as we all know the best allergy test is a history—I'll ask them to table the concern about allergy until the second visit. I suggest that we treat the skin first and correctly, without changing the diet, without worrying about dust mites and various other things. And then they come back and the child is better, but the environment hasn't changed, and the diet hasn't changed, and a lot of the allergy questions drift aside.

"Actually, I spend time redirecting patients away from worrying about food allergies—except in cases of specific, known food allergies, of course. I hear a lot of questions about tomatoes, gluten, dairy, and dust mites. I've actually been reprimanded. At the end of a long visit sometimes a patient will say, 'You didn't even tell me what to avoid in terms of grasses and molds and dust mites.'"

—Dr. Lio

If a child has severe AD, oftentimes I will leave no stone unturned at the first visit. That doesn't necessarily mean I will do an allergy test, but at least I will delve deeper.

Dr. Lebwohl: I do something similar. For the majority of patients, especially adults, diet plays very little role in AD. I will qualify that observation by saying that if a patient knows of a food that makes their AD worse, then obviously they should stay away from that food. But I think in most cases diet plays a very small role. So I try to get patients to focus on care of the skin.

Dr. Fivenson: I agree; I downplay food. Sometimes I will give patients the benefit of the doubt and order tests if they're insistent. Perhaps twice or three times a year in adults I find IgE levels for wheat. Avoiding wheat products and eating gluten free is such a fad these days, so I look those patients in the eye and say, "You don't have gluten disease, but perhaps wheat could be making your AD worse." But it's the exception. My mantra is "Moisturize, moisturize, moisturize, and, by the way, moisturize."

Dr. Lio: We've all had different training and experiences, we're from different geographic areas, some of us treat children and some of us treat adults, but the degree of convergence among us is pretty spectacular. It tells us that once you've been in the trenches with this disease, you learn how to fight it the hard way—and I think the right way.

What about probiotics? We have studies that show probiotics help and studies that show they don't do anything. I think this may

be a good example of a phenotypic difference in some patients. There may be a group of patients we don't yet know how to identify who respond well to probiotics. And then there are other questions: Which strain? How much? How frequently? And then, of course, who?

Do you routinely recommend probiotics?

Dr. Lebwohl: I do not routinely recommend probiotics. I think the jury is still out.

Dr. Fivenson: Nor do I.

Dr. Sidbury: Almost never. We have convergence again. I totally agree with your interpretation of the literature, Dr. Lio. There have been some recent systematic reviews and meta-analyses that have suggested there is more to probiotics that I have previously credited.[50-53] But the only time I recommend them in the setting of AD is for a child for whom I've had to prescribe more courses of systemic antibiotics for impetiginization than I've been comfortable with.

Dr. Lio: I actually do recommend them pretty routinely, but I don't think they make a major difference. I would say "watch this space." Hopefully we will learn more about the gut microbiome and its relation to the skin microbiome and cutaneous disease. An interesting study showed that if you sample the gut microbiome at 7 days of life, microbial diversity was significantly lower in infants who developed AD at 12 months of age.[54] But I feel that we're basically barbarians in the dark here. We have a lot to learn.

Dr. Fivenson: Actually, we should be barbarians in the dark, because back then they didn't have as much AD but they were exposed to more dirt and they had more diverse antigen exposure early on. In rural, agrarian areas, there is still lower AD incidence, presumably due to more diverse antigen exposures—a dirtier environment—leading to early desensitization in kids.

ATOPIC DERMATITIS IN ADULTS

Dr. Lio: Let's discuss the epidemiology of AD in adults, which is a somewhat contentious question. The estimated prevalence of AD in adults is generally cited as 1 to 3 percent.[55] A few years ago a paper found that the prevalence of AD in adults was 10 percent.[56] I was bowled over. What is your experience of AD in adults? What is the real prevalence?

Dr. Lebwohl: I think many adults have mild evidence of AD. So depending on how you define it, the number can vary tremendously. Does the person who had AD as a child and now presents with nummular eczema in the winter have AD? Does the person who had AD as a child and takes three hot showers each day in the middle of winter and then gets dry and itchy have AD? There are many manifestations, and I think you can come up with a number as high as 10 percent if you report everything as AD.

TABLE 3. POTENTIAL, EMERGING COMORBIDITIES OF ATOPIC DERMATITIS

Cardiovascular disease

Hypertension

Inflammatory bowel disease

Lymphoma

Obesity

Psychiatric disorders
- Anxiety
- Depression
- Suicidal ideation

Rheumatoid arthritis

Brunner PM, et al. J Invest Dermatol; 2017; 137: 18-25.[64]

Dr. Lio: I find that the presentation of AD in adults is different from the classic flexural pattern. Other than hand dermatitis or mild nummular dermatitis, the adults I see with AD tend to have more severe disease. They have more head and neck involvement, and, of course, hand involvement as well. They may have an erythrodermic presentation. AD lesions in adults are often more lichenified and drier. The burden of disease seems greater in adults with AD; many have terrible issues with quality of life. The International Study of Life with Atopic Eczema (ISOLATE) confirmed the profound effect AD has on quality of life in adults: 38 percent said the disease affected their choice of occupation; adults with AD took more sick days from work and were more likely to retire early. AD also has effects on sexual and social life: 43 percent felt awkward having a partner see or touch their body, and 58 percent reported avoiding social activities because of their disease.[57] I think AD is more difficult for adults. They have more responsibilities and quality-of-life issues, and the burden of disease is greater.

Dr. Fivenson: I think there are regional differences in the prevalence of AD in adults. In geographic areas with more dramatic winters, you see more flaring in adults.

There is a subset of AD patients that was described 10 to 15 years ago that I tend to believe in: head and neck AD (HNAD), in which people have fairly high IgE levels to normal flora and respond favorably to agents that lower those colony counts.

Dr. Lio: The role of Malassezia species in the exacerbation of HNAD has been investigated.[58] I see patients with this presentation and it's almost as if they have "seboeczema." One of my clinical pearls—it's not validated but it is my observation—is that philtrum involvement suggests HNAD. Those patients often do well with itraconazole pulses.[59] I don't see this pattern in children, but I do see it in young adults.

Dr. Sidbury: Since I'm a pediatric dermatologist, I've been conspicuously silent during the discussion of adult AD. But I see teenagers who are blending into a more adult pattern, and they may have an incredibly diffuse presentation, or their hands are quite involved, or they have HNAD. I do see that "seboeczema" pattern in teenagers.

Dr. Lio: Is AD a lifelong disease? Rob, you see children up to the teenage transition period. Does AD persist? Is there a J curve in which they have severe AD as children, then it gets better, and perhaps they get it again as adults? Or are childhood and adult AD two different diseases?

Dr. Sidbury: We all saw the 2014 paper that followed children in the Pediatric Eczema Elective Registry and showed that it wasn't until age 20 that 50 percent reported at least one six-month symptom- and medication-free period.[60] The provocative conclusion of the authors was that AD is likely a life-long disease.

I still believe that AD evolves, and I honestly and earnestly tell parents that my hope and expectation is that their child's AD will improve. In a child who has extensive disease, I'm a little more guarded, but I do expect that child to improve. I also tell parents that no matter how unaffected their child will be at age 25, he or she will never want a wool sweater for a birthday present. Certain sensitivities will be constant.

Dr. Fivenson: I'm in the camp that it's a lifelong disease. I think there is a large amount of oscillation, but clearly there's a subset of people who had it as children and tend to have it as adults.

Dr. Lebwohl: My experience mirrors what my colleagues have said. I do hold out the hope that AD gets better in adulthood. And certainly, in many patients it does. In many patients it clears up. But in some of them, or many of them, it actually comes back. Nowadays we have such a good treatment in the form of dupilumab, and hopefully even better treatments are coming. So I hope I can tell patients they'll grow out of it, but if it gets worse we have really good treatments that work for most patients.

ATOPIC DERMATITIS AND COMORBIDITIES

Dr. Lio: AD is a terrible disease by itself, but there are also recognized comorbidities associated with the disease. We talk about the atopic march, with allergy and asthma being part of this march. I think one of the most exciting developments is that the skin may be not only be the first piece on the march but also the most critical in terms of the pathogenesis of the march; epicutaneous or transcutaneous sensitization to allergens is part of what is driving other aberrant allergic responses.[61,62]

Recently many new comorbidities have been described. (Table 3). I think that attention deficit hyperactivity disorder is important, and I will often touch on this with parents, especially when a family is resisting treatment.[63] But we've also had comorbidities such as cardiovascular disease and obesity described recently.[64] What do you think of these emerging comorbidities. Should we talk to parents and patients about them?

" I'm a bit more in favor of the barrier repair agents, and I've recommended them more often as they've become more affordable. I think that convincing parents of the importance of moisturization is crucial, especially since there are good data showing that the application of a moisturizer to neonates in eczema-prone families prevents the development of AD."

—Dr. Fivenson

Dr. Lebwohl: I think the comorbidity story is less established in AD than it is in psoriasis. Asthma is certainly a well-established comorbidity, and when we treat severe AD with dupilumab it also works for asthma. But the association with other comorbidities, such as cardiovascular disease, is still in its infancy. Because the associations are not entirely accepted, entirely validated, I don't yet speak to patients about them. More work is needed so we can establish the validity of the comorbidities associated with AD, as we have established the comorbidities associated with psoriasis. Hopefully, in a few years we will also show that some of the new treatments for reversing AD are reversing those comorbidities as well.

Dr. Sidbury: I agree with Dr. Lebwohl. We have so much information to communicate to parents and patients during the first visit—skin care, bathing, everything we've been talking about—that including a discussion of comorbidities that we aren't certain are real but are entirely certain would be frightening is not valuable. It also isn't clear how we would intervene any differently. So I don't yet see any value in having that discussion.

The one "softer" comorbidity that I do consider is anemia. When kids come in and their parents say they're exhausted all the time and they're not concentrating in school, my immediate leap has always been to assume that they aren't sleeping well because they're itching so much. But in the back of my mind I wonder if they could

be fatigued because they are anemic. So I check their skin to see if they have pallor and sometimes I will pursue it further.

Dr. Fivenson: Over time, as we get better at treating AD, I think we will parse out the associated comorbidities. Perhaps they will be some of the same comorbidities that are associated with psoriasis because of the consequences of chronic immune stimulation.

Dr. Lio: I would like to thank my colleagues for this productive discussion. As I said when we began, this is an amazing time to be interested in AD, as our conversation has shown. ■

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FROM SYMPTOM CONTROL TO TARGETED TREATMENT: THE SHIFTING PARADIGM OF ATOPIC DERMATITIS CME QUESTIONS

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1. Which of the following statements best describes the mechanism of action of dupilumab?

A. Janus kinase (JAK) inhibitor that blocks the JAK 1 and 2 pathways
B. Phosphodiesterase 4 inhibitor
C. Fully human monoclonal antibody that blocks IL-4 and IL-13 signaling
D. Humanized monoclonal antibody that inhibits IL-31 signaling

2. What is the indication for crisaborole?

A. Second-line treatment of moderate-to-severe atopic dermatitis in adults and children 2 years of age and older
B. First-line treatment of moderate-to-severe atopic dermatitis in adults over the age of 18
C. Treatment of moderate-to-severe atopic dermatitis in adults and children 2 years of age and older who have failed therapy with a topical corticosteroid
D. First-line treatment of mild-to-moderate atopic dermatitis in adults and children 2 years of age and older

3. Which of the following potential atopic dermatitis comorbidities is supported by the strongest evidence?

A. Cardiovascular disease
B. Inflammatory bowel disease
C. Obesity
D. Attention deficit hyperactivity disorder

4. What was the most frequent treatment-related adverse effect, other than injection site reactions, in pivotal clinical trials investigating dupilumab?

A. Oral herpes
B. Induction of Crohn's disease
C. Conjunctivitis
D. Headache

5. What was the most frequent treatment-related adverse effect in pivotal clinical trials investigating crisaborole?

A. Cutaneous atrophy
B. Application site pain
C. Pruritus
D. Folliculitis

6. You are treating a 32-year-old woman who has been diagnosed with atopic dermatitis. She had atopic dermatitis as a child, but has not experienced significant symptoms since the age of 11. Her disease is now mild-to-moderate. She is experiencing significant pruritus as well as lichenification of the flexures, although her skin is not impetiginized. She asks for advice about bathing and showering. What would be the best response?

A. Take baths three times daily, soaking for more than 30 minutes and avoiding moisturizers
B. Take quick showers or baths with warm – not hot – water followed by the application of a moisturizer
C. Soak in a hot bath daily, washing vigorously with an antibacterial soap
D. Do not take showers or baths; take sponge baths once a week.

7. Based on a 5-point Likert scale, where 1 = not at all confident and 5 = completely confident, how confident will you be treating atopic dermatitis patients with the recently approved medications dupilumab and crisaborole now that you have completed this activity?

1 2 3 4 5

8. Based on a 5-point Likert scale, where 1 = not at all familiar and 5 = completely familiar, how familiar are you with the new and emerging targeted therapies for atopic dermatitis now that you have completed this activity?

1 2 3 4 5

9. Based on a 5-point Likert scale, where 1 = never and 5 = always, now that you have completed this activity, how often do you intend to recommend that your patients follow the "soak and smear" regimen: daily bathing followed by immediate application of a topical steroid ointment during intensive therapy or an emollient during maintenance therapy?

1 2 3 4 5

10. In order to help us assess your knowledge of select topics that were covered in this activity, please review the brief patient scenario and rate each of the statements as consistent with or inconsistent with your clinical approach.

You are treating a 26-year-old man with atopic dermatitis. He was originally diagnosed as an infant, and has experienced worsening of his condition over the past 2 years. He has been unresponsive to topical therapies as well as oral glucocorticoids, phototherapy, and cyclosporine. His disease has had a significant impact on his social and professional life. He does not date, and he is self-employed as an accountant because he is too embarrassed about his skin to work in an office environment. For the past 11 months he has been treated with mycophenolate mofetil. He originally had a good response, although he is currently experiencing partial relapse. His body mass index is 31 kg/m2.

- Increase the dose of mycophenolate mofetil
- Prescribe dupilumab
- Refer to a mental health professional
- Prescribe crisaborole
- Provide education on the association between atopic dermatitis and obesity
- Discuss the use of bleach baths

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Identify the mechanisms of action, efficacy, and safety of emerging targeted therapies for AD	_____	_____	_____
Recognize the lifestyle measures and daily skin care practices that are the foundation of an AD treatment plan	_____	_____	_____
Discuss the prevalence, presentation, and quality-of-life effects of AD in adults	_____	_____	_____
Interpret and explain the recognized and emerging comorbidities associated with AD in children, adolescents, and adults	_____	_____	_____

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME).

Name and email: _____

Do you feel the program was educationally sound and commercially balanced? ❒ Yes ❒ No

Comments regarding commercial bias:

_____

_____

Rate your knowledge/skill level prior to participating in this course: **5 = High, 1 = Low** _____

Rate your knowledge/skill level after participating in this course: **5 = High, 1 = Low** _____

Would you recommend this program to a colleague? ❒ Yes ❒ No

Do you feel the information presented will change your patient care? ❒ Yes ❒ No

Please identify how you will improve/change: _____

Change the management and/or treatment of patients. Please specify:

_____

_____

Create/revise protocols, policies, and/or procedures. Please specify:

_____

_____

Please identify the barriers to change.

_____ Cost ____ Lack of consensus or professional guidelines _____ Lack of administrative support _____ Lack of experience

_____ Lack of time to assess/counsel patients _____ Lack of opportunity (patients) _____ Reimbursement/insurance issues

_____ Lack of resources (equipment) _____ Patient compliance issues _____ No barriers _____ Other

Please specify: _____

To help evaluate this CME activity, may we contact you by email in 1 to 2 months to see if you have made this change? If so, please provide your email address below.

_____

_____

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