



## ASK THE PRESENTER

An editor from *The American Journal of Managed Care (AJMC)* sat down with Jonathan Silverberg, MD, PhD, MPH, in order to gain additional insight on the diagnosis, assessment, and management of atopic dermatitis (AD), with a focus on moderate-to-severe AD in adults in the clinical and managed care settings.

### *Q & A with Dr Silverberg*

*AJMC: Research demonstrates that diagnosing AD can be challenging, and current evaluation tools are not consistent across clinical practice. Can you describe for us what specific signs, symptoms, or risk factors you look for when making a diagnosis of AD?*

**DR SILVERBERG:** The first thing is to recognize the hallmark signs of AD, including erythema, calcification, scaling, excoriations or scratches that suggest the patient is scratching their skin, and dryness. Those are the 5 physical manifestations we look for in concert. Of course, the itch, another hallmark symptom of AD, must be present, as well; if it doesn't itch, it's not AD.

However, in dermatology, many chronic inflammatory skin disorders will have all of those different features. So the question is, how do you make a more specific diagnosis? The gold standard clinical guidelines used to diagnose AD are the Hanifin and Rajka Criteria, which look for a combination of 3 major and 3 minor criteria. I personally use them in my daily practice, but I recognize that in a busy practice setting, it can be difficult to do. In addition, there is the UK Working Party's Diagnostic Criteria. The use of formal criteria in clinical practice may be inconsistent, but many providers informally use these criteria even if they do not realize it.

Providers most commonly use the presence of flexural eczema to diagnose AD. Much of the time a patient presents with dermatitis localized to the flexural areas (meaning the creases of the elbows, backs of the knees, front of the neck, and ankles). However, some patients with AD do not have a flexural distribution, and that is where diagnosis can be more challenging. In those cases we look for a history of atopic diseases, like asthma, hay fever, food allergies, and family history of eczema, as well as age of onset.

*AJMC: How do you assess the level of severity once you determine your patient has AD?*

**DR SILVERBERG:** Right now, the gold standard for severity measures used in the field and considered to be the best by the Harmonising Outcome Measures for Eczema (HOME) group are the Eczema Area and Severity Index (EASI) and the Scoring Atopic Dermatitis (SCORAD). However, these are designed for clinical trials and not for clinical practice.

In clinical practice we do a few things that are analogous to certain components of the EASI and the SCORAD. One is stepping back and looking at the body surface area (BSA) and recognizing that, for example, a patient may have mild lesions, but they involve 80% of the BSA; with such extensive disease, the patient will almost always fall under the moderate-to-severe category. In addition, we assess the appearance of the lesions; a relatively thin plaque that is light red and not very thickened would be considered relatively mild. In contrast, a lesion that is oozing, weeping, and very thick, and has been there for a long time, would be considered moderate to severe, even when less extensive, such as 10% BSA. Another factor that comes into play is distribution. Even if the rest of the body is mild or moderate, if there is intense AD on the face, we might increase the severity assessment.

Further, there are patients with harmful functional outcomes. For many patients with AD on the bottom of the feet, the pain and itching can be so debilitating they are unable to go to work or school or perform daily activities. Similarly, AD can prevent patients from falling asleep or staying asleep at night. Even if the lesions may be mild to moderate on the rest of the body, when patients have such debilitating outcomes, we consider their disease to be more severe.



*AJMC: What are some of the new developments in our understanding of the pathophysiology of AD?*

**DR SILVERBERG:** This is a very exciting area right now. For years, there was a lot of back and forth about different mechanisms; but I think now, we are really starting to consolidate information and improve our understanding of AD. There are 2 major hallmarks of the pathophysiology of AD. One is the relatively older dogma about skin barrier and the impact of skin barrier on AD; this was recognized and brought to the forefront about 10 years ago with the discovery of genetic mutations of the skin barrier that caused a subset of AD.

Profound inflammation then occurs once the skin barrier is impaired. We have learned over the past few years that mediators of that inflammation include T-helper 2 pathways, particularly interleukin 4 (IL-4) and IL-13. In addition, there appears to be a subset of AD patients who also have involvement of other inflammatory pathways that include IL-22 and IL-17. It is also clear that there does not seem to be a role for immunoglobulin E (IgE) or IgG, which was debated for a while. I think this remains a little controversial, but evidence suggests these are not major players in AD. Further, IL-31 has been implicated as the link between inflammation and the sensation of itch in a subset of AD patients, and we have also learned that a signal called thymic stromal lymphopoietin appears to be the bridge between barrier disruption and the triggering of inflammation in the skin. These are all exciting pathways for therapeutic consideration.

*AJMC: Based on your epidemiology research, what are some of the trends with regard to the incidence and prevalence of moderate-to-severe AD among adult patients?*

**DR SILVERBERG:** That is a very hard question to answer. We don't have great trend data for whether or not the incidence and prevalence of moderate-to-severe AD among adults is increasing. We do have some evidence to suggest that the prevalence of AD in general, and more likely in kids, has steadily increased over the past few decades in the United States, and worldwide. However, most of that data came from survey-based research using self-reported outcomes.

We currently lack sufficient data on trends with respect to moderate-to-severe AD in adults. That being

said, from available data it appears that the prevalence has been relatively stable for this group. What we don't know is how time has affected the prevalence, or the proportion of those patients who present into their adult years, and whether or not there may be environmental or behavioral risk factors driving that. Our best estimates are that the prevalence and incidence of moderate-to-severe AD among adults has been steady.

*AJMC: What do you feel are some of the biggest challenges to managing moderate-to-severe AD in adults? How would you define uncontrolled AD?*

**DR SILVERBERG:** The key challenge is achieving optimal control of the disease. For that you really need to stratify your patients into different subsets. A very large subset of patients with AD have chronic disease. For those patients, one really needs to understand the clinical course of the disease and assess the number of flares and the number of days per year in which their skin is involved. Another challenge is preventing flare-ups so we're not constantly playing catch-up when flare-ups occur. One of our biggest unmet needs right now is having treatments with the efficacy we need, but also the safety so we can keep patients on it long enough to achieve long-term control.

One of the biggest challenges I face is controlling the itch. Antihistamines are commonly used, and I think some providers mistakenly think they will relieve the itch, but the evidence shows that they don't. They do help patients sleep through the itch, but that is where it ends. We don't yet have great options for controlling the itch unless we use immunosuppressant medications, which have several side effects. I would really love to see more treatment options for controlling the itch in patients with AD.

Uncontrolled disease to me is any moderate-to-severe disease activity that is not cleared by current treatment approaches within a given period of time or a given flare. If a patient is reporting itch for more than 3 days a week despite what should be optimal or adequate treatment—an itch that is profound, bothersome, and accompanied by other signs and symptoms of the disease—I would argue that the patient has uncontrolled AD, even if they are not in the middle of the flare. In such a case, I would initiate longer-term treatment approaches, such as proactive topicals or a systemic agent, in order to prevent flares and to suppress mild-to-moderate activity between flares.



*AJMC: How have moderate-to-severe AD patients generally been managed? How would you characterize the unmet need with regard to treatment in moderate-to-severe AD?*

**DR SILVERBERG:** Right now the simple answer is that the majority of patients with moderate-to-severe AD are generally being managed poorly. They are grossly undermanaged. They are also a challenging group to manage because it can take a significant amount of time to assess the burden of disease and truly understand how the disease affects a patient.

A key problem is that short-term approaches tend to fail in this subset, so there has been a need for long-term treatment options. Right now, most of the available treatments don't lend themselves well to long-term treatment because of safety and tolerability issues. It is very challenging to treat patients sufficiently in the standard practice setting.

If patients are being treated with systemic therapy, it is typically with systemic corticosteroids. The problem is that pulse dosing is commonly used, which is a short-term treatment approach. In other words, the current approach using systemic steroids is certainly not adequate at controlling AD. What often happens is that patients will either not fully clear with prednisone because they are not on it long enough, or they might respond very well in the short term but then have a rebound flare later and end up in worse condition after treatment. The question becomes, if patients are being treated with systemic agents, they may be able to achieve short-term control of the disease, but at what cost to their long-term health?

*AJMC: What are the advantages to patients when AD is treated as a chronic condition versus the approach of managing acute flares?*

**DR SILVERBERG:** I think there are several important advantages. First, if a patient's disease and their skin barrier are better controlled, they will have fewer infections overall. As a result, they will have fewer hospitalizations. They are not going to have as many missed workdays. In addition, there will be improvement in many of the other directly or indirectly related symptoms.

If you can adequately control the disease long term, you can improve patients' mental health and potentially decrease their mental healthcare utilization.

There are also interesting data that suggest chronic sleep disturbance in AD may be a major driver of some long-term health consequences. A while back we published a study looking at the association of AD and cardiovascular (CV) risk factors and CV disease, and one of the strong predictors was the presence of self-reported sleep disturbance. I think we are recognizing more and more the importance of trying to give these patients back their sleep to improve their long-term health.

Patient satisfaction is another big advantage. Right now, most patients with AD are undertreated, miserable, and/or barely functioning. When you give these patients back their life, it is so gratifying—it's unbelievable when patients say, "You saved my life."

*AJMC: Based on your experience, how does moderate-to-severe AD impact adult patients on a daily basis in terms of clinical symptoms, comorbidities, and quality of life?*

**DR SILVERBERG:** Most patients will have a daily itch even between flares and be scratching involuntarily throughout the day. They report profound flaking and scaling in the worst places and they're embarrassed. To add to the total distraction and inability to work or perform activities of daily living, many of our patients with moderate-to-severe AD also have comorbid allergic disease, like hay fever. They also typically have other allergies or sensitivities that may exacerbate their AD.

As for quality of life, as mentioned before, patients often suffer from mental health symptoms. Patients also often suffer serious injuries. One of my patients missed an appointment because she was in a car accident. This was her third car accident. I asked her what happened, and she said, "I am so distracted by my itch and I am so sedated from my antihistamine that I keep getting into accidents." Several of my patients have experienced workplace accidents because they were so distracted by their symptoms they made mistakes that left them injured.

In terms of social aspects and relationships, patients feel isolated. They avoid going out because they're embarrassed by the appearance of their skin, and they don't want other people to see them scratch. People often think they are contagious and don't want to be around them. Patients feel their disease negatively affects their romantic relationships, as well.



Patients with moderate-to-severe AD have problems in the workplace or at school. They are not able to wear the clothing they want to wear. They do not participate in recreational activities. They can't go on vacations in warm places because the heat aggravates their AD and itch. There are numerous ways in which AD affects patient quality of life.

*AJMC: How does the clinical burden of moderate-to-severe AD translate in terms of patients' productivity or ability to engage in normal activities?*

**DR SILVERBERG:** I'll give you the extreme scenario. I have more than a handful of patients who were previously on disability until we were able to get better long-term control of their AD with systemic agents, or who are still currently on disability because we have limited treatment options that are effective for controlling their moderate-to-severe disease. These patients cannot go to work at all.

Sometimes patients pursue career choices in which they deliberately avoid any kind of social interaction. Remember that many of the patients with moderate-to-severe AD in adulthood had it when they were adolescents, as well. The impact of AD during those formative years, how it impacted their overall development including mental health development, is very important.

Even with adult onset, the effects are significant. Some patients are unable to perform any kind of vigorous physical activity, are unable to go shopping, take care of their needs, go to work, or drive a car because of the distraction and embarrassment caused by their disease. I could go on for days about all of the different problems that we encounter, but I think those are a representative sample.

*AJMC: How would you compare and contrast AD with psoriasis for a payer?*

**DR SILVERBERG:** I think there are certain similarities in the sense that they are both chronic inflammatory diseases. They are both often associated with systemic inflammation and have a number of comorbid conditions that go along with them. However, I think the key difference between AD and psoriasis, which makes a difference in clinical practice, as well as for the payers, is the itch. Very few psoriasis patients experience an intense itch; it is more of a

cosmetic issue that has a major impact on quality of life. In contrast, all patients with AD experience itch, and patients with moderate-to-severe AD have extremely intense itch. On a scale of 1 to 10, they will generally report having a 10 out of 10 itch at least a few times a week. The burden of itch is a major difference between the 2 disorders. So, in my opinion, the burden of moderate-to-severe AD is far greater than that of psoriasis because of the enormous component of itch.

*AJMC: How would you characterize the strengths and limitations of current treatments for moderate-to-severe AD?*

**DR SILVERBERG:** It is hard to highlight the strengths of current treatment options because we have very few. Our approach right now is to try to maximize whatever topical treatment we can because the current systemic options carry risks of toxicity that are so great, we try to avoid them at all costs. The challenge becomes that we are unable to achieve adequate control of the disease.

You could argue that the topical approach is safer than the current systemic options. However, topical steroids have their own limitations and side effects. These are well established. We generally cannot keep patients on topical steroids with daily consecutive use for extended periods of time without running the risk of causing atrophy of the skin. Topical calcineurin inhibitors may cause burning and stinging, and they are often not effective enough as monotherapy; in fact, most of the time they are not effective as monotherapy for moderate-to-severe AD. All of the topical options are ineffective for really intense flares as monotherapy for my adult population.

Systemic steroids and some immunosuppressants typically work short term in a large subset of patients. The major limitation is that we cannot keep patients on them long enough to achieve long-term control, because even with short-term use patients experience major tolerability issues and side effects. With short-term use of systemic steroids, patients report insomnia and depressive symptoms. I've had a few patients admitted for psychosis related to systemic steroids. Over the long term, these agents can be devastating. So while they might work for a few weeks at a time, we just cannot use them safely for long-term control of the disease.



*AJMC: How involved should managed care organizations be in directing appropriate therapy for patients with uncontrolled moderate-to-severe AD?*

**DR SILVERBERG:** This is challenging to answer because, as with any treatment, there must be a certain level of cost consciousness in order to keep the current system afloat. I don't think there is a simple one-size-fits-all criterion or recommendation in the case of moderate-to-severe AD.

That being said, for patients who have failed everything previously (eg, some immunosuppressants and/or systemic steroids), it's a no-brainer that we should be open-minded in considering other treatment options. I think that for patients who require longer-term con-

trol, there are no other FDA-approved options at this time. When selecting a treatment option, there has to be a balance between regulating costs and ensuring that patients have access to drugs, especially when they are suffering.

When patients are miserable, they have very poor health outcomes. They have increased risk of mortality, increased risk of hospitalization, and many more problems that may very well be mitigated if they can gain access to newer systemic agents, and to some of the cutting-edge treatments currently in the pipeline. There is no question that managed care organizations have to be a part of the equation. We don't want to be too restrictive, because if we are, we may be hurting patients in both the short term and long term.

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