Severe atopic dermatitis poses a significant challenge to practitioners, particularly when mainstay therapies fail. And yet, these affected children can be least ignored, as their disease impacts multiple aspects of health, well-being, and daily personal and family life. Systemic therapy may be the best option for these cases, but determining the right candidates for such treatment is critical. This article will summarize the benefits and limitations of various systemic therapies, including those currently available and potentially forthcoming. Additionally, it will highlight compelling areas of study and research that are relevant to the evolving treatment paradigm of severe atopic dermatitis.

WHO SHOULD RECEIVE SYSTEMIC THERAPY?
Candidates for systemic therapy must have failed intensive topical and multimodal therapy and experience recurrent flares despite best efforts to gain control of disease. Patients are at minimum three to four years of age, and typically older, before meeting this criterion. Appropriate cases are those with frequent secondary infection, chronic moderate to severe disease with significant negative impact on school and/or home life, excessive use or inability to tolerate topical anti-inflammatory therapy, and prior failure or inability to treat with phototherapy. Overall, this applies to a small subset of patients, as the vast majority can be controlled with topical anti-inflammatories, emollients, and adjunctive methods such as wet wrap therapy, periodic bleach baths, and proactive maintenance. Superimposed allergic contact dermatitis might warrant consideration before systemic therapy, although patch testing is often difficult to perform in cases of severe, diffuse disease.

The current main approach to systemic management is suppression of the inflammatory response. Given this, several important steps should be taken in advance of prescribing therapy. Chief is a thorough discussion of the approach and potential benefits and toxicities of treatment options, followed by confirmation of parental and patient understanding and acquisition of treatment consent. All systemic agents are used off-label for atopic dermatitis, and very few head-to-head pediatric drug trials have been conducted. Risks requiring disclosure include organ toxicity, infection, and malignancy, although occurrence is infrequent (and very rare in the case of malignancy) with careful dosing and monitoring and limiting the duration of therapy. It is also important to elicit the ability of parents and patients to comply with treatment. Systemic therapy requires frequent clinic visits and lab monitoring a requisite for nearly all options. Moreover, as the drugs are pregnancy category C, D, or X, contraception for females of childbearing age should be considered before initiating therapy and periodic pregnancy tests performed during treatment. It is also essential to inform other relevant providers regarding the decision to start a systemic agent, as this may affect their care of the patient (e.g. need for avoidance of live vaccines, interference with allergy shots) and/or require their input and monitoring.

AVAILABLE AGENTS FOR TREATMENT
The main agents used for severe atopic dermatitis are systemic corticosteroids, cyclosporine, azathioprine, mycophenolate, and methotrexate. Other less common agents are interferon-gamma, intravenous immune globulin (IVIG), oral tacrolimus, and biologic agents.

According to the 2014 updated guidelines of care from the American Academy of Dermatology (in press), systemic treatment decisions should be based on each individual patient’s atopic dermatitis status (current and historical), comorbidities, and preferences. A major factor to consider in choice of agent is the acuity of disease compared to the time typically needed to observe positive effects. While systemic steroids, cyclosporine, and ultraviolet A (UVA)-1 phototherapy are generally considered faster acting, mycophenolate, azathioprine, and methotrexate tend to be a bit slower in effect, as is narrow-band UVB therapy. Concomitant medical therapies, co-existent infections, cost of therapy and insurance formularies, patient age, and parental opinion and concerns must also be factored.
Ahead are brief profiles of the potential benefits and limitations of available systemic therapies.

**Systemic Corticosteroids.** There are multiple risks with systemic corticosteroid use, such as rebound flares, hypertension, mood changes, infection, and arrhythmias and hypokalemia with IV pulsing. Long-term use is discouraged because of the well-known toxicities, which include negative effects on linear growth and bone density. Short-term courses, however, are usually inadequate for chronic disease control. Given these elements, systemic corticosteroids are generally not recommended, but are mainly reserved for “crises” or with the intent to bridge to another systemic agent or phototherapy.

**Cyclosporine.** Cyclosporine has the most evidence for efficacy, and has been shown to give improvement in as little as two to four weeks. A meta-analysis found the effects to be similar in adults and children. Side effects can include hypertension, elevations in serum creatinine, and gastrointestinal symptoms, though these may be less frequent in children. However, continuous therapy is not recommended beyond one to two years due to renal toxicity, while the number of short courses safe to give is unknown. In addition, there is a potential for relapse on discontinuation of therapy, with rates of 50 to 86 percent reported in some studies.

**Azathioprine.** Azathioprine has shown to be effective in children in several case series and one open-label, prospective 24-week study. Profound marrow suppression is a major concern, although dosing by thiopurine methyltransferase activity levels decreases occurrence. Gastrointestinal symptoms and elevations in liver transaminases may also be noted. Azathioprine can generally be used for longer periods (two to three years) than cyclosporine. It does carry a black box warning of association with hepatosplenic T-cell lymphoma, particularly with concomitant use with tumor necrosis factor (TNF)-alpha inhibitors or for greater than three years duration in the treatment of Crohn’s disease.

**Mycophenolate Mofetil.** Mycophenolate mofetil has been helpful for pediatric atopic dermatitis in a few retrospective case series. Higher per kilogram doses may be required in children, due to increased body surface area with younger age. Heller et al. recommends 1200 mg/m²/day. Treatment with mycophenolate may have less organ toxicity risks, and possibly less risk of neoplasia. However, as it is not used as much for non-cutaneous inflammatory conditions, there is the potential for less opportunity to evaluate risk. Mycophenolate also has a boxed warning of the occurrence of progressive multifocal leukoencephalopathy and now requires counseling on potential fetal risks and appropriate contraception for administration (the Mycophenolate Risk Evaluation and Mitigation Strategy system).

**Methotrexate.** With a long history of use for inflammatory skin conditions, methotrexate has the benefit of cumulative experience with its administration. Nevertheless, long-term efficacy for treatment of atopic dermatitis is not as well-documented as that for psoriasis. Typical weekly dosing and also more frequent dosing (i.e. 2.5mg four days per week) have been tried without difference. Importantly, methotrexate may be administered for longer periods. It may be less immunosuppressive at low doses, but does have potential for liver and rarely, pulmonary, toxicity.

In an open label, randomized 12-week trial in Egypt, 20 children were given low-dose methotrexate 7.5mg weekly and 20 were given low-dose cyclosporine 2.5mg/kg/day. Cyclosporine showed a more rapid onset (two to three weeks), but also more rapid relapse (average of 14 weeks), whereas methotrexate showed a more delayed onset (three to five weeks) and a later relapse (average 20 weeks). No further comparative data in children is available to date.

### OTHER OPTIONS

If patients do not respond or are not candidates for the previous therapies, other options exist, but with less experience with use.

**Interferon-Gamma Therapy.** Interferon-Gamma is a Th1 Cytokine used to reduce infection in chronic granulomatous disease. It may give a more balanced immune response in AD patients and older placebo-controlled trials showed benefits with use in children and adults with severe, unremitting disease. Some advocate using interferon-gamma over immunosuppressants in those with repeated infections such as eczema herpeticum. But fever and chills are common, and hypotension and tachycardia are sometimes reported at higher doses. In addition, it is a much more costly therapy relative to the above agents.

**Intravenous Immune globulin (IVIG).** IVIG blocks Fc receptors on antigen presenting cells and may also downregu-
A five-year-old with uncontrolled atopic dermatitis complicated by thick, excoriated nummular plaques and frequent Staph infections (including with methicillin-resistant *Staph aureus*) – at baseline and after 11 months of azathioprine therapy. He is now being tapered off to topical agents alone.

late T-cell activation. Studies have been limited and with mixed results. One randomized controlled trial in 40 children treated with 2g/kg/month for three months showed significantly reduced severity, but disease relapse occurred six months after discontinuation. 11. Frisch S, Siegfried EC. The clinical spectrum and therapeutic challenge of eczema herpeticum. Pediatr Dermatol. 2011 Jan-Feb;28(1):46-52.

**O**r**a**l Ta**r**acilum. In an open-label pilot study of 12 adult patients receiving oral tacrolimus followed by transition to topical tacrolimus, improvement in disease severity was noted. 12. It may also be an appropriate choice for those with repeated skin infections, but warrants additional supportive studies. IVIG is also limited by the need for monitored infusion.

**B**iologic A**g**ents. The use of biologic agents to treat severe eczema still remains to be realized. 13. Data on TNF-alpha inhibitors and omalizumab (an anti-IgE antibody) for atopic dermatitis management has been more negative than positive. Although some efficacy was noted with efalizumab and alefacept, both have been withdrawn from the market. The anti-CD20 (B-cell) agent rituximab and the anti-IL-5 agent mepolizumab have shown some positive effects, but have been limited to small case series. Clinical trials are underway, with results pending, for anakinra (an interleukin (IL)-1 receptor blocker), dupilumab (an IL-4 receptor-subunit antibody) and AMG 157 (which blocks thymic stromal lymphopoietin-receptor interaction). Hopefully, effective targeted therapies will come to fruition in the near future.

In terms of other new systemic therapies under study, the oral phosphodiesterase (PDE)-4 inhibitor apremilast has shown some promise. In an open-label study, adults with moderate to severe AD had decreased itch, improved QOL, and at the higher dose, improved disease severity (EASI) scores. 14. Pediatric studies would be an appropriate next step.

**O**ther D**i**rections of S**t**udy

Hopefully, additional trials and genetic/pharmacogenetic studies will provide insight into why some children respond to certain agents and not others. The Pediatric Dermatology Research Alliance (PeDRA) Inflammatory Skin Disease Collaborative is currently working to assess and better define characteristics of children with severe, refractory AD and is conducting a comparative observational study to provide additional efficacy and safety data on current systemic drugs.