

REVIEW

The role of *Malassezia* in atopic dermatitis affecting the head and neck of adults

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Atopic dermatitis is a common chronic skin condition. A subset of patients with head and neck dermatitis may have a reaction to *Malassezia* flora fueling their disease. Although there are no documented differences in *Malassezia* species colonization, patients with head and neck atopic dermatitis are more likely to have positive skin prick test results and *Malassezia*-specific IgE compared with healthy control subjects and patients with atopy without head and neck dermatitis. There is no clear relationship with atopy patch testing. The reaction to *Malassezia* is likely related to both humoral- and cell-mediated immunity. Clinically, *Malassezia* allergy may be suspected in patients with atopic dermatitis and: (1) head and neck lesions; (2) exacerbations during adolescence or young adulthood; (3) severe lesions recalcitrant to conventional therapy; and (4) other atopic diseases. There is literature to suggest that these patients will benefit from a 1- to 2-month course of daily itraconazole or ketoconazole followed by long-term weekly treatment. (J Am Acad Dermatol 10.1016/j.jaad.2008.07.058.)

Atopic dermatitis (AD) is a common skin condition affecting up to 18% of children and 2% of adults in the United States.^{1,2} People in the United States are estimated to spend up to \$3.8 billion annually on physician services and prescription drugs for the treatment of AD.¹ A subset of patients have severe AD that is refractory to conventional treatment with topical steroids and moisturizers. Within this group, there may be subpopulations of patients who would benefit from alternative or adjunct treatment strategies. One study in 1983 found that patients with AD of the head and neck improved clinically after treatment with oral ketoconazole.³ This spurred the study of *Malassezia* yeasts and their role in AD, particularly head and neck dermatitis (HND), a subtype of AD in which the head and neck areas are preferentially affected. This article reviews evidence for the colonization,

Abbreviations used:

AD:	atopic dermatitis
APT:	atopy patch test
DC:	dendritic cell
HND:	head and neck dermatitis
IL:	interleukin
MHC:	major histocompatibility complex
SPT:	skin prick test

immune response, clinical presentation, and treatment options for patients with *Malassezia* species as a contributing factor to their AD.

THE PRESENCE OF *MALASSEZIA* ON ATOPIC SKIN

Many studies have sought to find a differential pattern of *Malassezia* colonization on skin affected by AD compared with healthy skin.^{2,4-10} However, the published results are mixed (Table I). There is no convincing proof that the skin of patients with AD is more heavily colonized with *Malassezia* or is colonized with different species of *Malassezia*, when compared with healthy control subjects or patients with seborrheic dermatitis.

The challenges of proper sampling, in vitro culture, and correct identification of *Malassezia* species could have confounded some of the results creating the conflicting reports on *Malassezia* colonization patterns. First, studies used different sampling methods including contact plates, swabs, and tape strips. Second, studies used different culture media to grow the yeasts in vitro. Because

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Funding sources: None.

Disclosure: Dr Bechtel has been a paid consultant and is on speakers bureau for Genetech, Abbott, Centocor, and Biogen-Idec. Dr Zirwas has received honoraria from Coria Labs and Astellas Pharma. Dr Darabi and Ms Hostetler have no conflicts of interest to declare.

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Published online September 30, 2008.

0190-9622/\$34.00

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doi:10.1016/j.jaad.2008.07.058

Table I. Comparison of published research on cutaneous *Malassezia* colonization

Study	Patient sample, methods	Key findings
Nakabayashi et al, ⁵ 2000	17 Patients with AD, 64 patients with other dermatoses, 108 control subjects in Japan Skin swab cultures to describe colonization	Compared with healthy individuals, face and neck of patients with AD is more often colonized with <i>M furfur</i> and less often with <i>M globosa</i> and <i>M sympodialis</i>
Gupta et al, ⁴ 2001	31 Patients with AD, 79 patients with other dermatoses, 20 control subjects in Canada Quantitative contact plate cultures to describe colonization	AD and healthy skin are equally frequently colonized with <i>M sympodialis</i>
Sugita et al, ⁷ 2001	32 Patients with AD in Japan Nested PCR to describe colonization	<i>M furfur</i> , <i>M globosa</i> , <i>M restricta</i> , and <i>M sympodialis</i> are common to both patients with AD and healthy control subjects Microflora of patients with AD has more diversity AD and healthy skin show similar colonization rates with <i>M sympodialis</i> , <i>M obtusa</i> , and <i>M globosa</i>
Faergemann et al, ² 2002	Review article	AD skin is colonized by different genotypes of <i>M globosa</i> than healthy skin
Sugita et al, ⁸ 2003	32 Patients with AD and 20 control subjects in Japan DNA sequence analysis of <i>M globosa</i>	
Sugita et al, ⁹ 2004	13 Patients with AD and 12 control subjects in Japan DNA sequence analysis of <i>M restricta</i>	AD skin is colonized by different genotypes of <i>M restricta</i> than healthy skin
Sandstrom Falk et al, ⁶ 2005	124 Patients with AD, 16 patients with seborrheic dermatitis, 31 control subjects in Sweden Skin swab cultures to describe colonization	<i>Malassezia</i> growth was found in fewer patients with AD than in patients with seborrheic dermatitis or healthy control subjects ($P < .01$) Patients with AD had fewer positive culture results in lesional than in nonlesional skin ($P < .05$) <i>M sympodialis</i> dominated in patients with AD and in healthy control subjects
Sugita et al, ¹⁰ 2006	34 Patients with AD in Japan RT-PCR to quantify colonization	Head and neck is 7-12 times more colonized with <i>Malassezia</i> compared with trunk or limbs <i>M globosa</i> and <i>M restricta</i> account for 80% of all <i>Malassezia</i> colonization on any body part Other <i>Malassezia</i> are found in < 40% patients

AD, Atopic dermatitis; PCR, polymerase chain reaction; RT, real time.

Malassezia species have fastidious culture conditions and exceedingly different growth rates, one media may favor the growth of a certain yeast over another yeast.¹¹ Third, many studies have used qualitative rather than quantitative microbiological methods,⁴ making it difficult to assess the significance of skin colonization. Fourth, studies have been performed across the world and their variable results may indeed reflect colonization differences between samples obtained from different populations.

By minimizing these variables and using modern quantitative molecular techniques (eg, polymerase chain reaction–based terminal fragment length polymorphism analysis),¹² future research could obtain results that would be more comparable and provide a greater understanding of the colonization patterns of AD and HND.

THE IMMUNE RESPONSE TO *MALASSEZIA* IN PATIENTS WITH AD: SKIN PRICK TEST, SPECIFIC IgE, AND ATOPY PATCH TEST

Numerous clinical studies have measured the immune response of patients with AD to *Malassezia* antigens using the skin prick test (SPT), specific IgE, and atopy patch test (APT). It is important to note that these studies have not consistently compared the immunologic response to *Malassezia* with the immunologic response to other common cutaneous flora such as *Candida*, staphylococci, streptococci, and *Trichophyton*. Compared with healthy control subjects, patients with atopy are more likely to mount an immune response after exposure to an antigen. Therefore, the documented responses to *Malassezia* may be nonspecific. However, definitively establishing a relationship between HND and *Malassezia* would require an almost infinite battery

of microbial antigens in patients with HND, non-HND AD, and other inflammatory dermatoses, and healthy control subjects. Acknowledging these limitations, we will review the literature on the immunologic response to *Malassezia* in patients with AD with a particular focus on studies that also measured the responses to other skin flora.

The SPT and specific IgE examine the B-cell-mediated humoral response to an antigen. Several studies have shown that patients with AD react more frequently to *Malassezia* extract or recombinant *Malassezia* antigens on SPT and exhibit higher levels of *Malassezia*-specific IgE compared with healthy control subjects and patients with atopy without dermatitis.^{11,13-19} Focusing on the subset of patients with HND, research has shown that these patients tend to have higher rates of positive SPT results and higher levels of *Malassezia*-specific IgE when compared with patients who have AD without HND.^{13,17,19-25} The most favorable study enrolled 589 patients and found that 100% of patients with HND had increased *Malassezia*-specific IgE compared with only 13% of patients with AD without HND.²³ Two studies have even reported a correlation between *Malassezia*-specific IgE levels and the clinical severity of HND.^{23,25}

Two studies have compared the IgE response to *Malassezia* with the response to other skin flora. First, Scalabrin et al¹⁹ measured IgE specific for *M furfur*, *Candida albicans*, *T rubrum*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, and *Aspergillus fumigatus* in patients with moderate to severe AD, patients with asthma, and healthy control subjects. They found that patients with AD were 132 times more likely to have *Malassezia*-specific IgE than the asthmatics or healthy control subjects. Second, Nordvall et al¹⁷ recruited patients with high total serum IgE and AD, seborrheic dermatitis, tinea versicolor, or no apparent skin disease. They measured the levels of IgE specific for *M furfur*, *Candida albicans*, *T rubrum*, *Cladosporium herbarum*, *Staphylococcus aureus*, animal dander, deciduous tree pollens, grass pollens, and various foods. They found that *Malassezia*-specific IgE was specific for HND when compared with all other patients. These studies of SPT and specific IgE suggest that the immune system of patients with AD recognizes *Malassezia* antigens and induces a B-cell-mediated humoral response against these antigens.

In contrast, the APT assesses the T-cell-mediated response to an antigen. Studies of APT in AD have mixed findings.^{13,15,16,26} Some research has shown that patients with AD react more frequently to *Malassezia* extract and recombinant *Malassezia* antigens than healthy control subjects, patients with

atopy without dermatitis, or patients with other inflammatory dermatoses.^{15,16,26} One study comparing multiple skin flora reported that patients with AD were more likely to test positive to *Malassezia* than to *Candida* or *Dermatophagoides*, when compared with patients with vulvodynia or other dermatitis.²⁷ However, there is not a consistent correlation of HND with APT. There are two plausible explanations for this finding. It could be that T-cell-mediated immune reactions are less important in HND than IgE-mediated responses. It could also be that the APT may be a less sensitive test for demonstrating *Malassezia*-specific immune responses.

Some of the variability seen in the results of different studies may be related to the methodology of *Malassezia* extract storage, culture conditions, and selection of antigens. The stability of *Malassezia* extracts has been reported to be poor, even when stored at +4°C, and it is recommended that storage should not exceed more than 1 month.²⁸ Researchers have also observed that the culture period has an impact on the antigenic composition of *Malassezia* extracts and recommend that culture extracts containing the highest number of antigenic proteins should be used in clinical testing to avoid false-negative results.²⁹ Another interesting report demonstrates that the serum IgE of patients with AD binds both antigens that are *Malassezia* species-specific and antigens that are shared among different *Malassezia* species.³⁰ Thus, the use of different antigens, some that are species-specific and some that are shared among multiple *Malassezia* species, may contribute to the high degree of variability in reported reactivity against *Malassezia* species and certain antigens.

IMMUNOLOGIC BASIS FOR THE RESPONSE TO *MALASSEZIA* IN PATIENTS WITH AD

Thus far, we have outlined the laboratory evidence describing the immune reaction against the skin flora *Malassezia* that may be a factor contributing to some cases of refractory HND. It is also important to describe the molecular and cellular mechanisms of the interaction of yeasts with the host. Fig 1 illustrates a potential pathway for the altered skin barrier associated with AD and the increased *Malassezia* antigen load to stimulate both the innate immune system (keratinocytes, dendritic cells [DCs], and natural killer cells) and the adaptive immune system (T and B cells).

First, the keratinocytes of a patient with AD have a baseline barrier function defect as a result of altered filaggrin, an alkaline pH, decreased antimicrobial secretions, decreased IgA, and decreased sweat

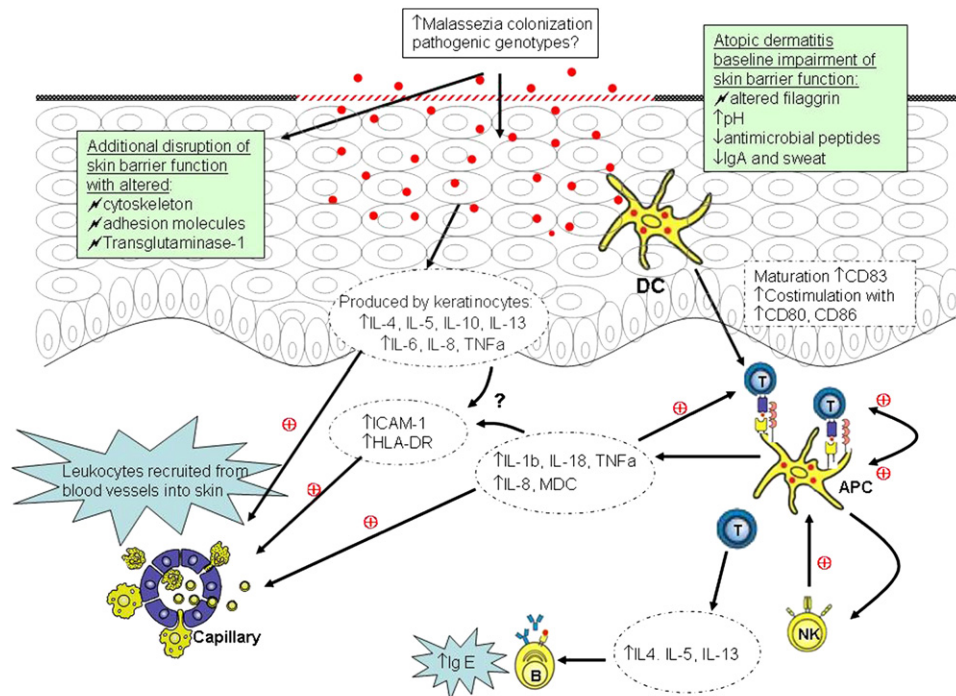


Fig 1. Overview of cellular and molecular mechanisms through which *Malassezia* species aggravate inflammation in patients with atopic dermatitis (AD). Colonization of sebaceous skin with *Malassezia* exacerbates barrier dysfunction of AD skin and facilitates skin penetration by *Malassezia* antigens. In response to dense *Malassezia* colonization, keratinocytes produce T-helper 2 cytokines and chemokines and local antigen presenting cells (APCs) are activated. Activated APCs take up *Malassezia* antigens and present them to T cells. T cell-APC interactions result in T-cell activation and production of additional T-helper 2 cytokines, chemokines, and up-regulation of adhesion molecules. This leads to influx of more leukocytes into *Malassezia*-colonized skin and enhances inflammation. During this process, B cells are also activated by APCs and T-helper 2 cytokines. This results in isotype switching and production of *Malassezia*-specific IgE. APC, Antigen presenting cell; B, B-cell; CD, cluster of differentiation; DC, dendritic cell; HLA, human leukocyte antigen; ICAM-1, intercellular adhesion molecule 1; Ig, immunoglobulin; IL, interleukin; NK, natural killer cell; MDC, monocyte derived chemokine; T, T-cell; TNF, tumor necrosis factor.

production.^{31,32} This baseline defect can be further compromised by *Malassezia*'s ability to impair the keratinocyte cytoskeleton, the adhesion molecules, and the gene expression of transglutaminase-1.³³ Further, the alkaline pH may stimulate the release of antigens from *Malassezia* and the decreased antimicrobial peptides may allow *Malassezia* to flourish.^{31,32} These factors may result in a significantly elevated burden of yeast antigens presented to innate and adaptive immune cells.^{33,34}

Next, the DCs likely take up the *Malassezia* antigens, mature, and present the antigens to T and natural killer cells. These cells enhance the ability of the mature DCs and the altered keratinocytes to produce proinflammatory and immune-regulatory cytokines.³⁵⁻³⁹ However, some studies have reported decreased production of proinflammatory cytokines

(interleukin [IL]-1 β , IL-6, tumor necrosis factor- α) after coculture of *Malassezia* with human keratinocyte cultures.^{33,40,41} These inconsistencies could be explained by differences in *Malassezia* species or cell lines used for culture, yeast to cell ratio, methods used to detect cytokine response (polymerase chain reaction vs enzyme-linked immunosorbent assay vs microarray). In patients with severe AD, research has consistently found higher levels of IL-8 and chemokines compared with healthy control subjects.^{35,36} These substances recruit immunocytes to inflamed tissues. Thus, the DCs of patients with AD may be more effective at inducing immune cell recruitment to and retention in atopic skin after *Malassezia* antigen exposure than patients without AD.

Third, after DCs present *Malassezia* antigens to T cells, the T cells likely up-regulate the DC function

and stimulate B cells to produce *Malassezia*-specific IgE.⁴² The DC function may be further up-regulated by natural killer cells. One study demonstrated natural killer cells were found in close contact with CD1a⁺ DCs from skin biopsy specimens of *Malassezia*-APT-positive AD skin lesions.⁴³ Another study found that DCs were more resistant to natural killer cell–induced cell death when they were incubated with *Malassezia* before contact with the natural killer cells.^{43,44} These findings suggest that exposure to *Malassezia* leads to an increase in DC activation in response to stimulation by T cells and interaction with natural killer cells.

Overall, *Malassezia* appears to stimulate the innate immune cells (keratinocytes, DCs, natural killer cells) and to cause expansion of the adaptive immune cells (T and B cells). Several studies have examined the interaction of *Malassezia* with: (1) blood- and skin-derived T cells; and (2) peripheral blood mononuclear cells. In contrast to isolated blood- or skin-derived T cells, the peripheral blood mononuclear cells are a fraction of the peripheral blood with the granulocytes removed; leaving mainly T cells, B cells, monocytes, and natural killer cells. The peripheral blood mononuclear cells of patients with AD with documented positive *Malassezia*-specific SPT result, IgE, APT result, or a combination of these have shown an increased proliferation and an increased production of inflammatory cytokines after exposure to *Malassezia* compared with cells from healthy control subjects.^{45–47} This suggests that the subpopulation of patients with AD and a *Malassezia*-specific immune response have increased activation and expansion of peripheral blood mononuclear cells.

Again, it is important to note the studies cited above do not compare the immune reaction to *Malassezia* with the immune reaction to other cutaneous flora, therefore, it is not yet established whether the in vitro immune recognition of *Malassezia* in AD is specific. However, research has demonstrated that the cutaneous flora *Malassezia* does not evade immune recognition. This provides a base for the theory that colonization of seborrheic areas of AD skin may result in inflammation of these areas.

SOURCE OF IMMUNOLOGIC REACTIVITY: CLASSIC MAJOR HISTOCOMPATIBILITY COMPLEX–RESTRICTED ANTIGEN PRESENTATION VERSUS SUPERANTIGEN STIMULATION

The above studies provide evidence of increased immunologic reactivity to *Malassezia* in certain patients with AD, but they do not trace the cellular source (T lymphocytes, B lymphocytes, monocytes, or natural killer cells) of measured cell proliferation

or cytokine production. This carries significant implications to support an underlying mechanism of classic major histocompatibility complex (MHC)-restricted antigen presentation or superantigen stimulation.

Several studies have examined the response of blood and skin T-cell clones or T-cell lines to *Malassezia* extract. One study reported that T-cell lines generated from the peripheral blood mononuclear cells of patients with AD and *Malassezia*-specific IgE produced more IL-4 and IL-5 after polyclonal stimulation and had a higher IL-4/interferon-gamma ratio than T-cell lines of healthy control subjects.⁴⁸ Another study used T-cell clones generated from IgE-positive AD blood and lesional skin and found that 29 of 36 T-cell clones were reactive to *Malassezia*.⁴⁹ They further reported that the majority of lesional skin-derived T-cell clones showed a T-helper 2 or T-helper 0/T-helper 2 cytokine profile in response to the yeast. These results suggest that the T cells are being activated by *Malassezia* antigens through classic MHC-restricted antigen presentation, rather than by a superantigen.

To further investigate the mechanism of a classic MHC-restricted antigen presentation versus superantigen stimulation, one study examined the T-cell receptor beta chain V regions of peripheral blood T cells of patients with AD compared with healthy control subjects.⁵⁰ The T-cell receptor beta chain V region is specific for the antigen presented to a T cell. An MHC-restricted immune response to the antigenic epitopes of *Malassezia* would result in activation and expansion of only a few T-cell clones. In contrast, superantigens would induce nonspecific expansion of at least 5% to 20% of all T-cell clones.⁵¹ This study found that the T-cell receptor beta V regions of circulating T cells of patients with AD did not differ from those of healthy control subjects,⁵¹ arguing against the superantigen hypothesis. The same study then stimulated the peripheral blood mononuclear cells with *Malassezia* and described the resultant T-cell receptor beta chain V regions. Compared with the original peripheral blood mononuclear cells, the *Malassezia*-reactive T-cell lines showed a decreased use of some beta V regions and increased use of other V regions.⁵⁰ This pattern of T-cell reactivity to *Malassezia* is more likely to be mediated by classic MHC antigen presentation than antigen-nonspecific T-cell receptor activation by a yeast superantigen.

Further studies are needed to detail the effect of *Malassezia* on skin-homing T cells. To date, research in this area has been limited by difficulties associated with obtaining skin specimens with sufficient cell quantities for in vitro studies. This could be avoided

by studying the abundantly available cutaneous lymphocyte antigen-positive skin-homing circulating T cells.⁵² Cutaneous lymphocyte antigen-positive memory T cells of patients with AD were shown to be in an activated state characterized by: (1) spontaneous ex vivo proliferation; (2) secretion of high amounts of IL-13-dominated T-helper 2 cytokines; and (3) the capability to induce IgE production in autologous B cells, although cutaneous lymphocyte antigen-positive T cells of healthy control subjects exhibited a more resting phenotype with borderline cytokine production and proliferation. As opposed to T cells from patients with AD, the T cells from healthy donors induced IgG4 (a T-helper 1 associated immunoglobulin isotype).⁵³ A major caveat of the aforementioned studies is that most fail to address the issue of immunity to other microbes that colonize the skin of patients with HND. To prove specificity of immunity to *Malassezia* in HND, it would be necessary to demonstrate negative testing results to other cutaneous microbes.

POSSIBLE PATHWAY FOR THE DEVELOPMENT OF HND

In conclusion, the following hypothetical scenario is attractive: at or after puberty, the *Malassezia* colonization on the head and neck area increases in density as a result of increased sebaceous gland activity and/or transformation of the predominant *Malassezia* genotypes. The endogenous impaired barrier function defect in AD and the changes in *Malassezia* colonization expose the immune system of patients with AD to *Malassezia* antigens. Some patients then develop T-helper 2 skewed B-cell- and/or T-cell-mediated immune reaction to these antigens, resulting in increased inflammation in the densely *Malassezia*-colonized areas causing the clinical entity of HND. Given the widely accepted multifactorial cause of AD, it is unlikely that immunity against *Malassezia* would be a single causative factor of HND, but it could be a triggering and perpetuating factor.

Alternatively, it would be remiss not to discuss the possibility that these in vivo and in vitro immunologic reactions to *Malassezia* in patients with AD are unrelated to disease activity, but are simply related to the fact that individuals with AD have an increased propensity to develop immunologic reactions to any antigen to which their skin is exposed. To demonstrate that cutaneous colonization with *Malassezia* is a causative factor in the HND subset of patients with AD, it would be necessary to demonstrate that reducing cutaneous colonization with *Malassezia* leads to a decrease in disease activity in this subset of patients with AD. In the ensuing sections, we review

the clinical findings and the documented responses of HND to antiyeast therapy.

CLINICAL SIGNS AND SYMPTOMS OF HND

The forehead, eyelids, and neck are almost constantly affected in patients with a *Malassezia* allergy (Fig 2).^{24,54} The majority of patients (up to 86%) report manifestations of AD in typical regions of the body as a child followed by flaring in the head and neck region at puberty or young adulthood.^{25,54} This correlates with the typical time of increased sebum production and potential fluctuation in *Malassezia* genotypes.^{3,24}

This clinical observation has been confirmed with laboratory testing that showed patients aged 12 years and older have a higher proportion of *Malassezia*-specific IgE,^{15,19,25,26,55-59} positive SPT results,^{15,55} and positive skin culture findings than patients younger than 12 years.⁵⁵ For example, only 5% to 15% of patients with AD aged 0 to 10 years had *Malassezia*-specific IgE, compared with 65% to 90% of patients aged 11 to 21 years in one study of patients with generalized AD.⁵⁵

Patients with *Malassezia*-driven AD may present with more severe disease and may be refractory to conventional treatment modalities.^{13,25,54,57,58} Two studies with more than 100 patients each showed that patients sensitized to *Malassezia* had more severe objective scoring of their dermatitis than those who were not sensitized.^{13,59} In addition, the most severe lesions are typically distributed in the head and neck region compared with the rest of the body.^{25,54} Finally, patients with concurrent allergic asthma and/or rhinoconjunctivitis may be at a higher risk for *Malassezia* hypersensitivity,^{17,60,61} although the data on this are conflicting.¹⁵ The increased frequency sometimes observed is likely indicative of a stronger tendency in those individuals to generate IgE to environmental allergens. It is important to note that individuals with allergic asthma and/or rhinoconjunctivitis and without AD consistently test negative to *Malassezia* IgE.^{16,21,24,60}

In summary, the patients with prototypical HND would have typical AD as a child. At or after puberty, their disease pattern would change, becoming more severe, and they would develop severe disease in the head and neck region. Once their disease became more severe and involved the head and neck regions, they would be much more recalcitrant to standard therapies with topical steroids and moisturizers.

Because *Malassezia* is a difficult organism to culture, there is no reliable method to confirm *Malassezia* overgrowth during clinical practice outside of the research setting. As a result, *Malassezia* overgrowth can only be suspected based on clinical



Fig 2. Head and neck dermatitis: 16-year-old boy with lifelong history of atopic dermatitis in his antecubital and popliteal fossae. At age 13 years, he developed severe dermatitis of head and neck area that did not respond to moisturizers, tacrolimus 0.1% ointment, pimecrolimus 1% cream, or multiple different topical corticosteroids of high, medium, or low potency. At his initial presentation (**A**), he had been using fluocinolone acetonide 0.1% oil daily on his face for several months. It is possible that oil application may have contributed as nutrient medium for *Malassezia*. Itraconazole (100 mg daily) was started. At his 1-month follow-up (**B**), his face was clear for first time in 3 years and he had discontinued all topical therapy.

findings. The response to therapy directed at *Malassezia* is the best confirmatory evidence that *Malassezia* overgrowth was clinically relevant in a given patient. A similar situation is presented with scabies. In many patients, the scraping results are unreliable and often negative so it becomes necessary to treat based on suggestive clinical findings alone. The therapeutic response then confirms the original diagnosis.

TREATMENT STRATEGIES

Ketoconazole and itraconazole are the most frequently studied therapeutic agents for patients with AD and *Malassezia* allergy (Table II). They are highly effective anti-*Malassezia* agents, with in vitro testing of 125 genotypes of 11 *Malassezia* species from patients with AD and healthy volunteers showing that all genotypes were susceptible to both itraconazole and ketoconazole.⁶² Further, tacrolimus was synergistic against *Malassezia* with either agent.⁶²

In vivo studies have shown significant efficacy for systemic ketoconazole and itraconazole in the treatment of patients with AD and *Malassezia* allergy. These agents have been associated with improvement in objective clinical scoring, decreased use of topical steroids, decreased *Malassezia*-specific IgE, and decreased total serum IgE.^{3,54,57,61,63-68} The most dramatic therapeutic responses have been shown in

studies that selected patients with HND, active lesions, sensitization to *Malassezia*, and elevated total serum IgE.^{57,64,66} For example, Ikezawa et al⁶⁶ found that 100% of his 40 patients on 100 mg of itraconazole daily for 8 weeks demonstrated improved clinical scores, decreased dose or strength of topical steroids, decreased *Malassezia*-specific IgE, decreased serum total IgE, and decreased eosinophil count. Further, Kolmer et al⁵⁴ documented a case series of 5 patients with very severe HND that was refractory to inpatient allergen avoidance and multiple standard therapeutic agents, including prednisone, azathioprine, vancomycin, and ceftazidime. These lesions were so severe that all patients except one had to discontinue their schooling or employment. When 100 to 200 mg of itraconazole daily was added to their treatment plan, all patients cleared completely within 6 months. Of note, two of 5 patients had failed systemic fluconazole and later responded to itraconazole.⁵⁴ This may be a result of itraconazole's broader spectrum of antifungal activity and its ability to concentrate in the skin.⁵⁴

Topical antifungal therapy has not yielded the same strength of results. One randomized, placebo-controlled study of patients with AD and HND provided a treatment group with twice-daily miconazole-hydrocortisone cream and twice weekly ketoconazole shampoo for 4 weeks.⁶⁹ The control group

Table II. Comparison of studies using antifungal treatment strategies for atopic dermatitis

Study	Inclusion criteria	Study design, No. of patients	Treatment protocol	Treatment outcome
Clemmensen and Hjørth, ³ 1983	HND AD Positive skin prick test result to <i>Pityrosporum orbiculare</i>	Double-blind, placebo-controlled, crossover 14 Patients	Ketoconazole for 4 wk	AD scores improved significantly with treatment Female patients had most significant improvement
Broberg and Faergemann, ⁶⁹ 1995	HND AD	Randomized, double-blind, placebo-controlled 53 Patients	Flucloxacillin 750 mg bid and hydrocortisone cream bid for 4 wk for all patients Miconazole combined with hydrocortisone cream bid and ketoconazole shampoo twice weekly in treatment group 26 patients	AD scores improved in all patients Treatment group had significantly decreased number of patients with <i>Pityrosporum ovale</i> colonization
Back et al, ⁵⁷ 1995	AD Positive IgE to <i>Pityrosporum orbiculare</i>	Prospective cohort 18 Patients	Ketoconazole 200 mg daily for 2 mo, then 200 mg twice weekly for another 3 mo for all patients	AD scores improved significantly <i>Pityrosporum orbiculare</i> —specific IgE and total IgE decreased significantly No patient had further AD improvement after reducing dose to twice weekly
Kolmer et al, ⁵⁴ 1996	Severe HND AD refractory to moisturizers, steroids, and antibiotics	Case series 5 Patients	Itraconazole 200 mg daily added to patients' multidrug regimen for 4-6 wk Inpatient allergen avoidance and restricted diet for 4 patients	AD improved significantly in all patients After 6 mo of therapy, one patient was able to return to work for first time in 6 years One patient had failed prior trial of fluconazole (100 mg daily), another failed 200 mg daily
Back and Bartosick, ⁶¹ 2001	AD Positive IgE to <i>M furfur</i> Elevated total IgE	Randomized, double-blind, placebo-controlled 29 Patients	Ketoconazole 200 mg daily for 3 mo for treatment group of 15 patients Placebo for 14 control subjects	AD scores improved in all patients; however, improvement in treatment group was independent of use of topical steroids <i>M furfur</i> —specific IgE and total IgE significantly decreased with treatment

Continued

Table II. Cont'd

Study	Inclusion criteria	Study design, No. of patients	Treatment protocol	Treatment outcome
Lintu et al, ⁶⁴ 2001	HND AD Positive IgE to <i>Pityrosporum ovale</i> and/or <i>Candida albicans</i>	Randomized, double-blind, placebo-controlled 75 Patients	Ketoconazole 200 mg daily for 1 mo for treatment group of 36 patients Placebo for 39 control subjects	AD scores improved significantly in treatment group Most significant improvement was found in patients who were female, had <i>Pityrosporum ovale</i> —positive culture results before therapy, and/or had elevated total IgE
Ikezawa et al, ⁶⁶ 2004	Moderate-to-severe HND AD	Randomized, crossover 34 Patients	Itraconazole 100 mg daily for 2 mo, placebo for 2 mo Group A (19 patients) received itraconazole for the first 2 mo, group B (15 patients) for second 2 mo	AD scores improved significantly in both groups during treatment Dose/strength of topical steroids, <i>M furfur</i> —specific IgE, total IgE, and eosinophil count also decreased significantly during treatment
Svejgaard et al, ⁶⁷ 2004	HND AD No steroids for ≥ 1 mo No antifungal for ≥ 2 mo	Randomized, double-blind, placebo-controlled 53 Patients	Itraconazole 400 mg daily (17 patients), 200 mg daily (18 pa- tients), or placebo (18 patients) for 7 days with 105 days of follow-up	AD scores improved significantly in head and neck distribution in both treatment groups, but only 8 of all 35 patients treated had $> 50\%$ improvement

AD, Atopic dermatitis; *bid*, twice a day; HND, head and neck dermatitis.

was maintained with twice daily hydrocortisone cream. Although there was no significant change in clinical scores between the groups, the quantity of *Malassezia* colonies decreased significantly in the treatment group. The authors hypothesized that treatment was not long enough to see the clinical benefit of topical antifungals.^{57,69} A more recent, double-blind, placebo-controlled study reported significant clinical improvement in AD scoring after 1 month of twice daily ciclopiroxolamine cream.⁷⁰ The conflicting results may be a result of patient selection, as the former study only required that patients with AD have HND, whereas the latter study required that patients with AD have HND and high levels of *Malassezia*-specific IgE. The improvement in the second study may be related to a subpopulation more likely to have *Malassezia* driving their AD, thus more likely to respond to topical antifungal therapy. It is also possible that ciclopiroxolamine was a more effective anti-*Malassezia* agent than the miconazole-

hydrocortisone cream, and that this resulted in the improved clinical response to ciclopiroxolamine.

The improved efficacy of systemic antifungals compared with topical agents may be related to several factors including better penetration into the hair follicle, better compliance, and better coverage of the entire skin surface. These factors may eliminate potential *Malassezia* reservoirs more readily and thus prevent rapid repopulation. It is also possible that the effects of systemic agents could be mediated by actions other than their antiyeast activity. However, if this were true, we would expect all types of AD to respond to systemic antifungals, rather than the specific response seen only in HNDs.

For dosage, almost every study to date has used 200 mg daily of ketoconazole or 100 to 200 mg daily of itraconazole.^{3,54,57,61,64-69} One month is typically the minimum time period required for therapeutic effect in most patients, and the first parameters to improve are itching and total area affected by

dermatitis.^{17,61} Lesions of the head and neck usually respond first and may show significant improvement after only 1 week of therapy.⁶⁷ After discontinuing antifungals, some studies have shown persistence of therapeutic effects for up to 3 months.^{64,66} After that time, regrowth of *Malassezia* occurs with relapse of symptoms.⁶⁴ The best regimen appears to be daily dosing for the first 1 to 2 months, followed by twice weekly dosing for as long as indicated by clinical severity. Following this protocol, Back et al⁵⁷ showed significant clinical and laboratory improvement after 2 months of daily ketoconazole and continued therapeutic effect with 3 months of twice weekly ketoconazole, although no further improvement was noted at the twice weekly dosage.

Because of the potential hepatotoxic effects of these agents, it is important to assess liver function before initiating therapy. If the results are normal and the patient does not have known liver disease, no additional monitoring is required during itraconazole therapy. However, all patients treated with ketoconazole require regular monitoring for evidence of liver toxicity. Patients with known or suspected liver disease should consider systemic therapy only with close monitoring.

SUMMARY

In summary, *Malassezia* allergy should be suspected in patients whose AD: (1) includes head and neck lesions; (2) worsened during adolescence or young adulthood; (3) is severe and recalcitrant to therapy; and (4) is associated with other concurrent atopic diseases. There is significant literature to suggest that these patients will benefit markedly from a 1- to 2-month course of daily itraconazole or ketoconazole followed by chronic treatment with twice-weekly itraconazole or ketoconazole. In cases in which oral therapy is contraindicated or not warranted, twice-daily therapy with topical ciclopiroxolamine cream may be useful.

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