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CONTINUING PROFESSIONAL DEVELOPMENT PROGRAM

Malassezia yeasts in the pathogenesis of atopic dermatitis

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SUMMARY

Atopic dermatitis is a common skin condition, the aetiology of which is multifactorial, involving genetic, immunological and environmental factors. In recent years, it has been suggested that various microbial organisms may also be involved in the pathogenesis of the disease. Yeasts belonging to the *Malassezia* genus have received particular attention. These yeasts, known to be a part of the normal skin flora, have been shown to be capable of inducing immunoglobulin (Ig)E-mediated and T-cell mediated immune responses postulated to contribute to chronic inflammation in the skin, particularly in the head and neck region, where colonization with *Malassezia* is the greatest. Considerable evidence now exists to support this idea, raising the possibility that specific antifungal therapy may be a useful treatment measure in some atopic patients who have a head and neck pattern of dermatitis.

Key words: atopic eczema, head and neck dermatitis, *Pityrosporum orbiculare*, *Pityrosporum ovale*.

INTRODUCTION

Atopic dermatitis (AD) is a common skin condition, the exact cause of which remains unknown. A multifactorial aetiology is postulated, with genetic, immunological and environmental factors all thought to be relevant to the pathogenesis.[1] A genetic predisposition to the atopic state, defined as an inherited tendency to develop immunoglobulin (Ig)E antibodies to specific allergens, has been associated with the disease,[2] implying that type I immune mechanisms could be relevant to the pathogenesis.

In addition to specific immune mechanisms, a central feature of AD that may also play a key part in the pathogenesis of the condition is the presence of itch. AD patients are considered to have a reduced itch threshold, and so are more likely to develop itch in response to very mild stimuli, including aggravation of skin barrier function by irritants.[3] This increased tendency to itch is important because numerous factors may trigger itching, which can lead to an itch–scratch cycle, resulting in repeated physical aggravation of the skin that ultimately provokes new lesions or leads to a worsening of existing dermatitis.[4]

Although patients with AD will commonly display elevated serum IgE levels to a wide range of allergens, the relative importance of each as a contributing pathogenic factor in the skin has remained uncertain.[5] Skin exposure to aeroallergens such as house dust mite, cat dander and grass pollens can provoke dermatitis in some patients.[6] Specific food allergy may play a part in paediatric patients.[7] In addition to these, microbial organisms have also been implicated as important factors.[8,9] Increased colonization and frank secondary infection of the skin of AD patients with *Staphylococcus aureus* has been well documented, as have specific interactions of this bacterium with the host immune system.[9] Some studies have suggested that *Candida albicans* may also have a possible pathogenic role.[10]

In recent years, there has been growing evidence that yeast organisms belonging to the *Malassezia* genus (previously termed *Pityrosporum*) may also be involved in the pathophysiology of AD. These yeasts are considered to be part of the normal skin flora. It has been proposed that AD patients, particularly those with dermatitis localized in the head and neck region (an area of the body known to be heavily colonized by *Malassezia*), react specifically to these organisms, leading to skin inflammation that may exacerbate the underlying dermatitis.[11]

We review the current literature that has investigated the potential role of *Malassezia* yeasts in the pathogenesis of AD, including studies that have examined the possible use of antifungal therapy as a treatment measure in AD patients.

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MALASSEZIA YEASTS

Malassezia yeasts were first identified in the late 1800s, but have since been described in many subsequent studies that have used different names to refer to the same organism. Early descriptions of the organism were based mainly on morphological criteria, and the two main forms of the yeast that were described were the oval form, referred to as *Pityrosporum ovale* and the round form, named *Pityrosporum orbiculare*. These two forms have been considered by some to represent a different stage in the cell cycle of the same organism.[12] Current nomenclature, however, favours the term *Malassezia* for the genus, with more extensive biochemical and molecular characterization having now identified seven distinct species (*Malassezia furfur, Malassezia pachydermatis, Malassezia sympodialis, Malassezia globosa, Malassezia slooffiae, Malassezia restricta and Malassezia obtusa*).[13] Despite this, some authors have continued to use the older terms of *P. ovale* and *P. orbiculare* when referring to the yeast in the medical literature. (In this article, the term *Malassezia* will be used when discussing the yeast.)

Malassezia yeasts are lipophilic organisms. They are a permanent component of the microflora of normal human skin, although they are less common in the prepubertal years.[14–16] They usually reside on skin as saprophytes, and can be cultured from almost all body areas. The highest concentrations of the organism are found on the skin of the face, scalp, neck, upper chest and back; the presence of high amounts of sebaceous skin lipids is thought to favour the growth of the organism in these sites.[15–18] Generally, skin colonization with *Malassezia* increases after puberty, which is presumably related to the increase in skin surface lipids that results from higher sebaceous gland activity during this period. Colonization reaches a maximum in the third decade of life, and then decreases in middle-aged and elderly individuals, possibly because of decreasing skin lipid content.[19]

Although generally considered to be non-pathogenic, *Malassezia* yeasts can, under appropriate circumstances, cause skin diseases such as pityriasis versicolor and folliculitis, and have also been associated with seborrhoeic dermatitis.[20,21] The exact pathogenic mechanism of the organism in each of these diseases, however, is uncertain, and may differ between each condition. In pityriasis versicolor, *Malassezia* undergoes a change from its inert spore form to a mycelial form that is associated with an inflammatory reaction in the skin.[22] In *Malassezia*-related folliculitis, overgrowth of the yeast deep within hair follicles is thought to provoke an immune response via local occlusion and the release of pro-inflammatory products.[23] In seborrhoeic dermatitis, impaired cell-mediated immunity may be a factor in the disease process.[22] In all these conditions, clinical benefit can result from appropriate antifungal therapy.

IMMUNOLOGY OF *MALASSEZIA* IN ATOPIC DERMATITIS

The idea that *Malassezia* yeasts could play a possible role in the pathogenesis of AD was first proposed more than 15 years ago, when researchers investigating atopic adults with head and neck dermatitis (HND) discovered that such patients displayed greater rates of positive skin-prick tests (SPT) to *Malassezia* (28%) than did AD patients with dermatitis distributed in other body sites (6%).[24] Supporting this hypothesis at the time was an earlier report that antifungal therapy for HND patients had resulted in a definite clinical improvement in the condition.[25] Since then, numerous groups have continued to investigate the theory that *Malassezia* yeasts might somehow be involved in triggering or exacerbating dermatitis in AD patients through direct stimulation of immune pathways, causing inflammation in the skin. The existing evidence suggests that both IgE-mediated and T-cell mediated immune reactions could be involved, and is outlined below.

Immunoglobulin E-mediated responses and *Malassezia*

The presence of IgE-mediated type I hypersensitivity to *Malassezia* in AD patients has been well documented by studies that have used radioallergosorbent testing (RAST) to detect specific IgE antibodies to the yeast. The prevalence rate of these antibodies appears to vary with age, being much higher in patients who are more than 12 years old (43–93%)[26–31] compared with patients of younger age (22–39%).[32–34] Antibody levels peak at approximately 20 years of age.[35] These same studies have also shown that *Malassezia*-specific IgE antibodies are almost non-existent in normal healthy individuals and only very rarely occur in patients with other *Malassezia*-related diseases, such as seborrhoeic dermatitis and pityriasis versicolor.

Patients with AD affecting mainly the head and neck region appear more likely to possess *Malassezia*-specific serum IgE antibodies compared with patients with AD located in other sites, with one study reporting rates of 100% and 13.6%, respectively, in these subgroups.[36] Interestingly, *Malassezia*-specific IgE is rarely detectable in atopic patients who do not suffer dermatitis.[28,31,32,37] Furthermore, in AD patients, the prevalence of type I hypersensitivity towards *Malassezia* tends to be much greater compared with that of other fungi.[29,33,38] These findings collectively imply that specific anti-*Malassezia* antibodies may be pathologically relevant and not just simple markers of atopy.

In addition to serum IgE detection, SPT has also been widely used to demonstrate the presence of type I hypersensitivity to *Malassezia*. Studies using SPT with *Malassezia* extracts have reported positive prevalence rates varying between 44% and 79% in AD patients older than 12 years of age, with normal healthy controls and atopic patients without a history of dermatitis usually having much lower rates (0–5%).[31,34,38–42] The biological activity of circulating *Malassezia*-specific IgE antibodies has also been confirmed by histamine release tests using serum from AD patients, which have been positive in approximately 70% of patients, and negative in normal controls.[38,40]

Cell-mediated responses and *Malassezia*

In vitro studies have shown *Malassezia* to induce much higher reactivity in the T cells derived from AD patients, compared with healthy controls, with these T cells being found to be of the T-helper (Th)2 type.[43] Similarly, in AD patients who have positive *Malassezia* RAST tests, *Malassezia* has been shown to stimulate greater production of Th2-related interleukin (IL) cytokines such as IL-4 and IL-10 by peripheral blood mononuclear cells compared with patients who are RAST negative.[44]

The presence of *Malassezia*-induced T cell reactivity has also been demonstrated using modified epicutaneous patch testing, which has shown that direct contact with *Malassezia* can induce an eczematous skin reaction in sensitized AD patients.[27,34,39,45] Although patch testing is traditionally used in the diagnosis of type IV contact allergy, some researchers have proposed the term 'atopy patch test' to describe an epicutaneous test performed in a similar manner to standard patch testing, but instead using allergens known to elicit type I IgE-mediated reactions.[46] The atopy patch test has been shown to produce strong positive skin reactions in atopic patients but not in non-atopic normal controls, with positive responses involving allergen-specific T cell activation and proliferation.[47,48] This suggests that traditional type I allergens may possibly also be involved in triggering type IV immune mechanisms.

Other immune responses induced by *Malassezia*

Other pro-inflammatory actions of *Malassezia* include its ability to strongly activate the alternative complement pathway[49] and to directly stimulate keratinocytes to produce inflammatory cytokines such as tumour necrosis factor (TNF)-α, IL-6 and IL-8.[50] *Malassezia* can also induce maturation of dendritic cells and increased production of TNF-α, IL-1β and IL-18 by these cells.[51,52] Apart from IgE, other antibody-mediated immune responses are thought to be less important, because *Malassezia*-specific IgG antibodies are detected only at low levels in AD patients, and can be found with a similar frequency in healthy normal people.[26]

PROPOSED PATHOPHYSIOLOGY OF *MALASSEZIA*-RELATED ATOPIC DERMATITIS

The pathophysiology of AD, in general, involves complex immunological interactions and is still not completely understood.[5] IgE-mediated responses against specific allergens are thought to play some part in inducing skin inflammation through immediate and late-phase hypersensitivity mechanisms.[53] Cell-mediated responses involving allergen-specific Th2 cells may also contribute to skin inflammation in AD, secreting cytokines (IL-4 and IL-5)

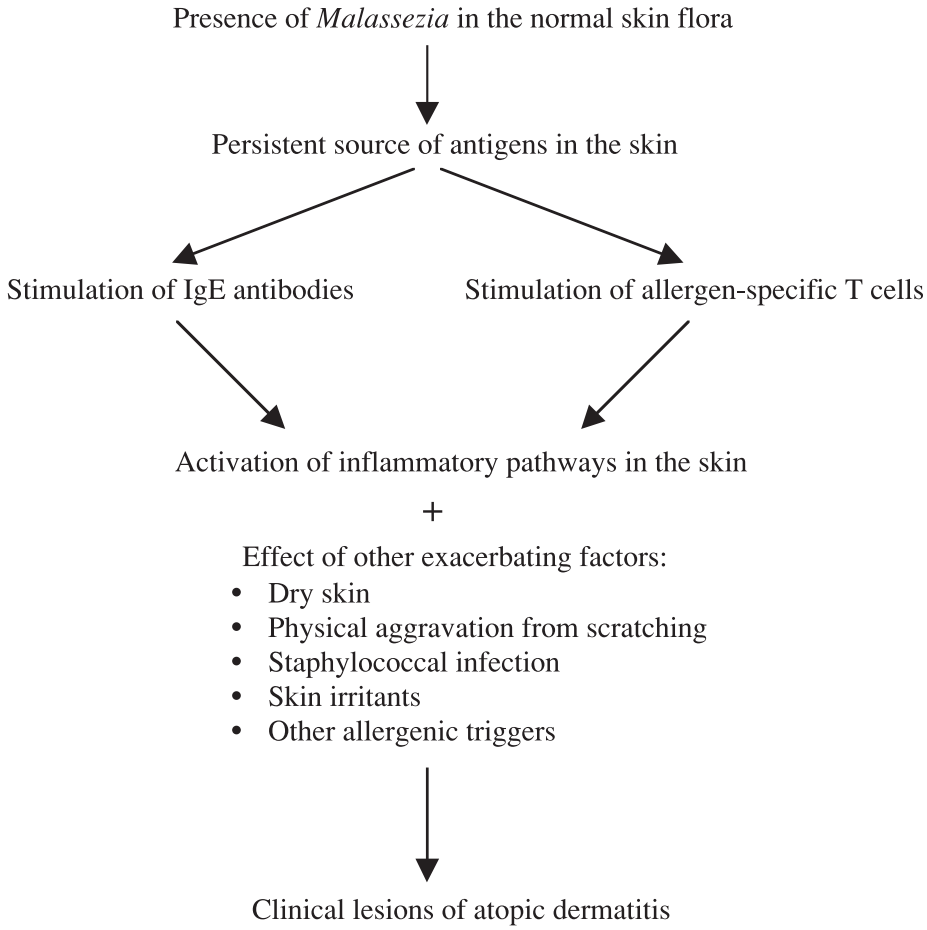

Figure 1 The postulated pathogenic role of Malassezia in atopic dermatitis.

which can further promote IgE responses.[54] Allergen binding to IgE receptors on Langerhans cells[55] may also be involved in specifically stimulating T cells, resulting in a cascade of responses that could sustain chronic inflammation in the skin.

Various studies suggest that a difference may exist between AD patients with type I hypersensitivity to *Malassezia* and those without. AD patients who have *Malassezia* IgE antibodies have been reported to exhibit a more active pattern of dermatitis compared with those who lack these antibodies.[33,56] Such patients are also more likely to have dermatitis present in the head and neck region and to display higher dermatitis severity scores compared with *Malassezia* IgE-negative patients.[24,29,35,36,39,42,57,58]

Based on the above findings, one theory outlining the possible pathogenic mechanisms involved in AD of the head and neck region is as follows. *Malassezia* yeasts, through their ability to stimulate IgE-mediated and cell-mediated responses, may be playing a part in triggering a variety of immunological mechanisms that lead to skin inflammation (Fig. 1). Initial binding of the yeast to Langerhans cells via IgE receptors could result in T cell sensitization via antigen presentation. Subsequent IgE-associated activation of allergen-specific T cells would stimulate cell-mediated immune responses involving mainly Th2 cytokine expression. This could be augmented by immediate type I hypersensitivity responses from direct stimulation of IgE-bearing cells, such as mast cells, and additionally through *Malassezia*-induced complement activation and keratinocyte cytokine release. All of these mechanisms could cause itch, which in turn would cause scratching leading to further skin barrier dysfunction and inflammation. These effects could also be worsened by other factors that aggravate atopic skin disease. Continuous exposure to *Malassezia* via the normal skin flora could then be responsible for repeated triggering of the host immune system, leading to recurrent skin inflammation. Because colonization of the organism is greatest in the head and neck area, the higher antigenic stimulus in this site would provoke a greater inflammatory reaction locally, which could explain why HND patients develop a more prominent form of AD in this specific region of the body.

EVIDENCE FROM TREATMENT STUDIES

If *Malassezia* yeasts do play a significant role in the pathogenesis of AD, then the group of patients that would appear to be most likely to respond beneficially to antifungal treatment would be those patients who possess demonstrable type I hypersensitivity to *Malassezia* and who have dermatitis localized predominantly to the head and neck region. Although a variety of antifungal drugs, which can be used topically and orally, are known to be effective against *Malassezia* yeasts,[59,60] very few appropriately designed studies have been carried out to evaluate the clinical efficacy of antifungal therapy in this subgroup of AD patients.

An early randomized controlled study involving 19 *Malassezia* SPT-positive AD patients with predominant HND first reported that oral ketoconazole (200 mg daily) in the treatment group ($n = 9$) produced a significant clinical improvement ($P < 0.005$) after 4 weeks, compared with placebo ($n = 10$).[25] Others have reported using oral itraconazole with good response in five patients with severe AD refractory to conventional therapy.[61] In an open study of 20 *Malassezia* IgE RAST-positive AD patients (which included patients who had both generalized dermatitis and HND), 5 months of treatment with oral ketoconazole (200 mg daily for 2 months then 200 mg weekly for 3 months) resulted in a significant improvement in clinical dermatitis scores post treatment compared with baseline ($P < 0.01$) and a reduction in both total serum IgE and *Malassezia*-specific IgE ($P < 0.05$), although no statistically significant correlation could be found between clinical improvement and the reduction in *Malassezia*-specific IgE.[30] A subsequent randomized, double-blinded, placebo-controlled study involving 29 *Malassezia* IgE-positive AD patients who were treated for 3 months with either oral ketoconazole 200 mg daily ($n = 15$) or an oral placebo ($n = 14$) also showed that *Malassezia*-specific IgE levels decreased significantly with antifungal treatment ($P < 0.01$), but the authors could not demonstrate a statistically significant difference in clinical outcome between the control and treatment groups based on assessment using the severity scoring of AD (SCORAD) index.[62]

Although topical antifungal medications can also reduce the presence of *Malassezia* on the skin,[41,63] very few studies have investigated their efficacy in AD patients. Some early anecdotal reports have suggested that bifonazole cream could produce clinical improvement in some patients with HND.[24] In a double-blinded, randomized, controlled study involving 53 AD patients who had dermatitis both in a generalized body distribution and in the head and neck region, half of the group ($n = 26$) were treated with ketoconazole shampoo twice weekly and a combination cream of miconazole and hydrocortisone applied twice daily for 4 weeks, while the placebo group ($n = 27$) were treated with hydrocortisone cream alone and a placebo shampoo.[41] The clinical dermatitis scores improved in all patients, although no statistically significant difference in dermatitis scores could be found between the two groups.

ATOPIC DERMATITIS AND *MALASSEZIA* ALLERGY: WHY IS THE CLINICAL RELEVANCE UNCLEAR?

Although the above treatment studies have failed to reliably demonstrate the clinical relevance of *Malassezia* allergy in AD, various reasons may explain the inconclusive nature of the findings to date. One particular problem has been with respect to patient selection. Most studies have involved only small patient numbers, and furthermore have not appropriately selected patients with predominant HND, the main subgroup of AD in which type I hypersensitivity to *Malassezia* is specifically thought to be clinically relevant. In one study, only 55% of AD patients who were selected to participate in a treatment trial had positive *Malassezia* skin-prick tests.[41] This is important to note given that the appropriate target group of AD patients for whom treatment may be beneficial is those patients who have both dermatitis

localized to the head and neck region and demonstrable type I hypersensitivity to *Malassezia*.

Another area of difficulty has been with respect to evaluating the clinical outcome of therapy. A variety of different methods can be used to score the severity of AD clinically, and although the SCORAD index is one available method that has undergone extensive validation,[64] it is designed to assess dermatitis globally on the body, and may not be the most appropriate method of assessing dermatitis purely in the head and neck region, the main body site postulated to be most affected by *Malassezia*-induced skin inflammation. Consequently, studies that have sought to demonstrate an effect of treatment in HND have been limited by the lack of properly validated methods of assessing dermatitis specifically in the head and neck area, making it more difficult to ascertain the efficacy of antifungal therapy on this particular target site.

With the advent of more improved techniques for culturing and identifying *Malassezia* yeasts, recent studies have also found that variation exists in the types of *Malassezia* strains that colonize human skin. In one study of normal Japanese subjects, *M. globosa* was found to be the most common species, whereas in the lesional skin of AD patients, *M. furfur* was found to be more prevalent.[65] Others have identified *M. sympodialis* as the most frequently identified strain on normal human skin and from lesional skin in AD patients.[13,18] New *Malassezia* species, as well as different genotypes of the same species, continue to be isolated from the skin of both normal healthy individuals and patients with AD.[66,67] These observations are important to consider because significant differences can exist in the susceptibility of the various *Malassezia* species to the commonly used antifungal agents, implying that any measurable improvement in dermatitis that is reliant on eliminating *Malassezia* from the skin could also depend on selecting the most appropriate antifungal medication for a given species.[68]

Finally, one further consideration is that, despite the ability of *Malassezia* to stimulate IgE antibody production, identifying the most important IgE-binding components of the yeast itself has been difficult. Different studies have demonstrated multiple IgE-binding proteins on the yeast, with the molecular weights (MW) of these varying from 12 kDa to >200 kDa.[38,69–72] Some studies have identified common antigens with the highest IgE-binding affinity, but even these have varied in MW from 9 kDa to 96 kDa.[69,71,73–75] Expression of these antigens can vary considerably among the different *Malassezia* strains.[76] Although species-specific and common antigenic IgE-binding components may be present, not all will bind to the serum IgE of all AD patients.[76] Studies that have used RAST testing have demonstrated that the sera of AD patients can display selective IgE binding to different *Malassezia* species, and that RAST allergens prepared from only one species of *Malassezia* may not detect IgE antibodies in some patients who have become sensitized to a different species.[42,77] Thus, it is possible that false-negative tests could result if a specific batch of *Malassezia* allergens is used to conduct type I hypersensitivity testing (SPT or RAST) in patients whose skin may be colonized with *Malassezia* strains that produce a different set of antigens. These patients could therefore have IgE antibodies with different specificities that may not readily bind to the antigens contained in the test solution. Variations in the prevalence of allergenic reactivity to fungi using SPT or RAST have been shown to exist between commercially manufactured and individually prepared fungal extracts.[78] This could explain the variable rates of *Malassezia* IgE-positive results in HND patients that have been reported by different studies to date, making it difficult to draw firm conclusions on the clinical relevance of type I hypersensitivity to *Malassezia*.

CONCLUSION

The hypothesis that *Malassezia* may play a part in the pathogenesis of AD has received credible support from many studies that have documented the possible pathogenic relevance of this organism. It is also apparent that atopic patients with a pattern of dermatitis that preferentially affects the head and neck region are significantly more likely to demonstrate positive tests for type I hypersensitivity to *Malassezia* compared with patients who have AD in other body sites and atopic patients without skin disease. Although this evidence suggests that *Malassezia* could be a pathogenic factor in a certain group of AD patients, the specific role of antifungal therapy in AD, at this point in time, remains inconclusive. Further properly designed studies involving the appropriate selection of patients and appropriate measures of clinical outcome are needed to definitively determine whether antimycotic treatment can be a useful therapeutic option in some patients during the course of their often chronic and therapeutically challenging disease.

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Continuing Professional Development Program

Select the most correct answers — multiple answers possible for questions 1–11

1. Atopic dermatitis (AD) patients are considered to have:
   a. A genetic predisposition to the atopic state.
   b. A reduced itch threshold.
   c. An inherited tendency to develop immunoglobulin (Ig)G antibodies to specific allergens
   d. Increased colonization with *Staphylococcus aureus*.
   e. Reduced levels of IgE
2. *Malassezia* yeasts are:
   a. Not part of the normal skin flora
   b. Separate and distinct from *Pityrosporum* yeasts
   c. Currently divided into seven distinct species
   d. Lipophobic.
   e. Generally considered non-pathogenic.
3. Skin colonization by *Malassezia* yeasts:
   a. Increases after puberty.
   b. Is favoured by low amounts of sebaceous skin lipids.
   c. Peaks in the third decade of life.
   d. Is common in prepubertal years.
   e. Is highest on the hands and feet
4. *Malassezia* yeasts have been associated with the following diseases:
   a. Pityriasis rosea.
   b. Seborrhoeic dermatitis.
   c. Pityriasis alba.
   d. Folliculitis.
   e. Pityriasis versicolor.
5. IgE antibody levels to *Malassezia* yeasts:
   a. Are almost non-existent in normal healthy individuals.
   b. Are highest in children under 12 years of age.
   c. Are high in all atopic individuals
   d. Are particularly increased with active flexural atopic dermatitis
   e. Correlate with type I hypersensitivity to other fungi.
6. Type I hypersensitivity to *Malassezia* yeasts can be documented using:
   a. Radioallergosorbent testing.
   b. Skin-prick testing.
   c. Histamine release tests.
   d. Culturing *Malassezia* yeasts from the skin of atopics.
   e. Ames test.
7. Cell-mediated responses to *Malassezia* yeasts:
   a. Involve T-suppressor cells.
   b. Involve T helper (Th)2 type T cells.
   c. Are highest in atopic patients with negative *Malassezia* radioallergosorbent testing results.
   d. Involve stimulation of release of cytokines such as interleukins 4 and 10.
   e. Show higher reactivity in AD patients compared with healthy controls.
8. Other immune responses induced by Malassezia yeasts include:
   a. Strong activation of the classic complement pathway.
   b. Stimulation of the production of tumour necrosis factor-γ by neutrophils.
   c. Stimulation of all antibody classes.
   d. Induction of maturation of dendritic cells.
   e. Inhibition of inflammatory cytokine production by keratinocyte.
9. The pathophysiology of AD probably involves:
   a. Immediate and late-phase hypersensitivity mechanisms.
   b. IgE-mediated responses to specific allergens.
   c. Allergen-specific Th2 cells.
   d. Binding of allergens to IgE receptors on Langerhans cells.
   e. Stimulation of cytokine release by Th2 cells.
10. Treatment studies using antifungal drugs in AD should involve:
    a. Patients with demonstrable type 1 hypersensitivity to *Malassezia*.
    b. Patients with generalized AD.
    c. Drugs known to be effective against *Malassezia* yeasts.
    d. Double-blinded randomized placebo-controlled trials.
    e. Small patient numbers.
11. Successful treatment trials of AD have included the use of:
    a. Topical ketoconazole.
    b. Oral ketoconazole.
    c. Topical itraconazole.
    d. Oral itraconazole.
    e. Topical amphotericin B.

Directions for questions 12–23. For each numbered item, choose the appropriate lettered item. There is only one correct answer to be chosen, but the same letter can be chosen more than once in any question.

With respect to questions 12–15:
   a. *M. globosa*.
   b. *M. furfur*.
   c. *M. sympodialis*.
   d. *M. pachydermatis*.

12. Lesional skin of Japanese AD patients.
13. Skin of normal Japanese subjects.
14. Lesional skin of non-Japanese AD patients.
15. Skin of normal non-Japanese subjects.

With respect to questions 16–19:
   a. Significant clinical improvement compared with placebo.
   b. No significant difference between two active treatment groups.
   c. Significant reduction in *Malassezia*-specific IgE levels.
   d. Clinical improvement in head and neck dermatitis.

16. Hydrocortisone 1% cream, ketoconazole shampoo and miconazole cream.
17. Oral ketoconazole 200 mg/day for 4 weeks.
18. Oral ketoconazole 200 mg/day for 3 months.
19. Topical bifonazole.

With respect to questions 20–23:
   a. Keratinocytes.
   b. T cells.
   c. Mast cells.
   d. Langerhans cells.

20. Stimulation of T cells follows the binding of *Malassezia* yeasts to IgE receptors on these cells.
21. Antigen presentation causes sensitization of these cells.
22. Immediate type I hypersensitivity response results from direct stimulation of these cells.
23. Immediate type I hypersensitivity response follows cytokine release by these cells.

The correct answers for the questions published in Vol. 45, No. 3, are as follows:

1. c, e	9. a, c, d	17. c
2. d	10. a, b, c, d, e	18. a
3. b	11. c, d	19. b
4. a, c, d	12. a	20. c
5. a, c, d	13. c	21. b
6. a, b, e	14. d	22. d
7. b, d, e	15. b	23. a
8. a, c, d	16. d	

The Australasian College of Dermatologists

Continuing Professional Development Program
Category I

Australasian Journal of Dermatology
Volume 45, No. 4, 2004

Name: . . . . . **CPDP No.:** . . . . . .

State: . . . . . .

Questions 1–11
Circle the most appropriate answers — multiple answers possible. Each question must have all correct answers circled in order to receive points.

1.	A	B	C	D	E
2.	A	B	C	D	E
3.	A	B	C	D	E
4.	A	B	C	D	E
5.	A	B	C	D	E
6.	A	B	C	D	E
7.	A	B	C	D	E
8.	A	B	C	D	E
9.	A	B	C	D	E
10.	A	B	C	D	E
11.	A	B	C	D	E

Questions 12–23
Circle the correct answer.

12.	A	B	C	D
13.	A	B	C	D
14.	A	B	C	D
15.	A	B	C	D
16.	A	B	C	D
17.	A	B	C	D
18.	A	B	C	D
19.	A	B	C	D
20.	A	B	C	D
21.	A	B	C	D
22.	A	B	C	D
23.	A	B	C	D

Pass Mark: 75% (if you obtain this mark or higher you will be granted 1.5 hours Category 1 CPDP credit).

If you feel the need to indicate ambiguity in a question, please do not write comments on the answer sheet.

Please return your answer sheet to College by 1 January 2005. Answer sheets received after this date will not be accepted.