Allergology International (1997) **46**: 125–133

Original Article

Efficacy of oral amphotericin B for refractory atopic dermatitis with specific IgE to *Candida albicans* and food allergens in sera

Kazuko Kitamura,[1] Chizuka Suga,[1] Sumi Onuma,[1] Toshiko Kawaguchi,[1] Fusae Yamazaki,[2] Hiroshi Suguro[2] and Zenro Ikezawa[1]

[1]Dermatological Department, Yokohama City University Urafune Hospital and [2]Yokohama Children's Allergy Center, Yokohama, Japan

Abstract

The efficacy of oral amphotericin B (ApB) was studied in 125 cases of refractory atopic dermatitis (AD). Indications for ApB therapy were positive CAP-RAST (Pharmacia & Upjohn Co. Ltd)-class to *Candida albicans* and several food allergens and a high intake of sweets or alcoholic beverages together with recalcitrant symptoms of AD, such as facial erythema and eruptions refractory to topical steroids. Good or excellent results were obtained in 56.8% of 125 cases. Assessment of improvement in the 125 subjects was statistically compared with that in 55 controls who were not treated with ApB. There were no significant differences in the background between the two study groups. Cases treated with oral ApB showed significantly greater improvement ($P < 0.01$) than did the controls, who were not treated with ApB, over 3 and 6 month periods. Treatment with ApB helped patients to discontinue or to reduce the frequency of topical steroid use or to change from high-dose steroids to lower-dose steroids. Treatment of patients with oral ApB resulted in improvements in laboratory data, including CAP-RAST to *C. albicans* and several food allergens. Good results were associated with restricting the intake of food allergens. A poor response was recognized in patients with a significantly high titer of CAP-RAST levels to *Dermatophagoides farinae*. Controlling environmental allergens and limiting exposure to food allergens was necessary to achieve success with ApB treatment.

Key words: amphotericin B, antifungal therapy, atopic dermatitis, *Candida albicans*, food allergy.

Introduction

The pathogenesis of atopic dermatitis (AD) has not yet been clarified and is supposed to be multifactorial. In treating AD, the majority of practitioners have found that AD is controlled by avoiding allergens and irritants, taking care of dry skin, eating a balanced diet and managing stress, together with application of topical medication and systemic anti-allergic drugs. However, management of AD refractory to conventional therapy remains controversial. Efficacy of antifungal therapy[1–4] has been reported for recalcitrant AD. It is well known that *Candida* species are normal commensals of humans and one of the most common causes of internal infection.[5] Concerning *Candida* sensitization and skin disease, in some cases of urticaria,[6] *Candida albicans* has been reported to be a pathogenic factor. A principle in treating allergic diseases resulting from fungi is the avoidance of fungi as allergens. *Candida* spp. live in our environment but are mainly found internally, especially in the digestive tract, as one of the microflora.[5] Therefore, to avoid *Candida* as an allergen, administration of an anti-*Candida* drug is advisable. Matsuda *et al.*[1] suggested that colonization of *Candida* in the digestive tract and

Correspondence: Dr Kazuko Kitamura, Department of Dermatology, Yokohama City University Urafune Hospital, 3–46 Urafunecho, Minamiku, Yokohama 232, Japan. Email: <kitadrm@mbainfoshere.or.jp>

Received 27 June 1996. Accepted for publication 21 February 1997.

sensitization to *Candida* may be involved in aggravation or persistence of recalcitrant AD and they reported the efficacy of oral nystatin (Ny), an anti-*Candida* drug. Suga *et al.*[7] also reported the efficacy of anti-*Candida* drugs on refractory symptoms of AD and emphasized that combining a restricted diet for food allergy with antifungal therapy affects the efficacy of the drugs. However, there has not yet been a control study performed to assess the efficacy of anti-*Candida* drugs. Nystatin and ApB are polyene antifungal drugs, damaging the cell membrane of fungal cells, and their absorption through the gastrointestinal tract is highly limited.[8] Amphotericin B has a better minimal inhibitory concentration than Ny.[8] The present study assessed the efficacy of anti-*Candida* therapy using oral ApB in treating patients who failed to respond to conventional therapy and statistically compared improvement in these patients with that in controls who did not receive ApB therapy.

METHODS

Subjects and their background characteristics

The present investigation was performed between June 1992 and September 1995. The subjects of the study were 125 outpatients (61 males and 64 females) with AD in the outpatient clinic of the Dermatological Department

Table 1. Clinical and laboratory data of patients receiving oral ApB (group I) and those not receiving oral ApB (group II)

	Group I	Group II	*P* value
Clinical data			
No. patients	125	55	
Male (%)	61 (48.8)	29 (53)	
Female (%)	64 (51.2)	26 (47)	0.6274*
Age (years)†	19.8±1.0	19.0±1.5	0.5216**
Duration of AD (years)†	13.6±9.0	14.9±1.0	0.1832**
No. patients according to severity of AD			
Moderate (%)	35 (28)	15 (27)	
Severe (%)	90 (72)	33 (60)	0.8555*
No. patients according to types of eruptions‡			
Flexural (%)	109 (87.5)	51 (92.7)	0.0461*
Facial (%)	121 (96.8)	50 (90.9)	0.1515*
No. patients adhering to restrictions of food allergens (%)	62 (49.6)	29 (54.7)	0.815*
Laboratory data			
Total serum IgE (IU/mL)†	6394±688	9279±1406	
No. patients with IgE ≤ 5000 IU/mL (%)	72 (58.5)	25 (46.3)	
No. patients with IgE >5001 IU/mL (%)	51 (41.5)	29 (53.7)	0.1319*
CAP-RAST levels to *C. albicans* (UA/mL)†	18.7±2.3	14.0±3.7	
No. patients with CAP-RAST levels ≤ 3.5 UA/mL (%)	44 (35.5)	18 (32.7)	
No. patients with CAP-RAST levels 3.5–10 UA/mL (%)	31 (25)	16 (27.1)	
No. patients with CAP-RAST levels ≥ 10 UA/mL (%)	49 (39.5)	21 (38.2)	0.8427*
CAP-RAST levels to *Df* (UA/mL)†	158.9±30.5	187.2±48.7	
No. patients with CAP-RAST levels ≤ 20 UA/mL (%)	37 (31.6)	13 (24.5)	
No. patients with CAP-RAST levels 20–90 UA/mL (%)	32 (27.4)	19 (35.9)	
No. patients with CAP-RAST levels ≥ 5 UA/mL (%)	48 (42)	21 (39.6)	0.4676*
Sum of positive CAP-RAST class to food allergens†§	2.8±0.3	3.6±0.5	
No. patients with CAP-RAST ≤ 0.75 UA/mL (%)	39 (32.5)	18 (33.3)	
No. patients with CAP-RAST 0.75–5 UA/mL (%)	48 (40)	13 (24.1)	
No. patients with CAP-RAST ≥ 5 UA/mL (%)	33 (27.5)	23 (42.6)	0.0693*
Candida spp. cultured from feces			
No. specimens	56	45	
No. positive (%)	19 (33.9)	10 (22.2)	0.1962*

*χ^2 test; **Mann–Whitney *U*-test. †Data are presented as the mean±SEM.
‡Flexural, flexural surface; facial, head, face, upper neck, upper chest, back type. §Egg white, cows' milk, soy bean, wheat, rice.
AD, atopic dermatitis; ApB, amphotericin B; *C. albicans*, *Candida albicans*; *Df*, *Dermatophagoides farinae*.

of Yokohama City University Urafune Hospital, Yokohama Children's Allergy Center and an affiliated clinic. In these subjects diagnosis of AD was compatible with the definition and diagnostic criteria for AD given by the Japanese dermatological association.[9] Clinical and laboratory characteristics of the patients are given in Table 1. The mean patient age was 19.8 years (range: 2–51 years) and the mean duration of AD was 13.6 years. Working criteria of AD severity referred to the grading of the clinical severity proposed by Miyakawa *et al.*[10] By this criteria, 71.8% of patients had severe AD and the remaining 28.2% had moderate AD. Eruptions were of the flexural surface type in 87.5% of patients, of the head–face–neck–upper chest–upper back type in 96.8% of patients and of the erythroderma type in 34.1% of patients. Baseline laboratory data for these patients were as follows: the mean (±SEM) total serum IgE was 6394±688 IU/mL, the mean (±SEM) CAP-RAST-levels to *Dermatophagoides farinae* (*Df*) and *C. albicans* were 158.9±30.5 and 18.7±2.3 UA/mL, respectively, the sum of CAP-RAST-class to five representative food allergens (including egg white, cows' milk, soy bean, wheat and rice) was 2.8±0.3 UA/mL. The mean lactate dehydrogenase (LDH) value, which reflects the severity of AD,[11] was 575±20.3 IU/L.

Oral ApB for recalcitrant AD

The prescription used for the oral treatment of recalcitrant AD with ApB was ApB (Fungizone®, Bristol-Myers Squibb K.K.) at 300–600 mg/day, *Clostridium butyricum* MIYA–BM® fine granules (Miyarisan Pharmaceutical Co. Ltd) at 2.0–3.0 g/day and a vitamin B complex at 2.0 g/day. This prescription combined ApB with *C. butyricum* MIYAIRIC to inhibit the disturbance of normal flora in the gut and with a vitamin B complex to prevent vitamin deficiency; in addition, the intake of food allergens was restricted and foods, such as sweets, which facilitate *Candida* growth were avoided and a low yeast diet was maintained.

Overall assessment of treatment response

Overall assessment was made by evaluating the improvement in subjective and objective symptoms, examining the doses of topical steroids used and noting the side effects of ApB. Patient responses to ApB treatment were classified as excellent, good, fair and useless or worse according to the following working criteria:

(1) Excellent: a marked improvement was noted and no topical steroids were needed on the face or on other lesions and no topical medicaments, skin care products or topical steroids of a milder class were used or were used on only a small area, depending on the subject.
(2) Good: a definite improvement was noted, no topical steroids were used on the face or on other lesions and non-steroidal medicaments or topical steroids of a milder class were used in part.
(3) Fair: a slight but insufficient improvement was noted, and patients became controllable with standard therapy, including topical steroids conventionally used.
(4) Useless: symptoms were not improved by treatment or became worse and topical medicaments were not able to control refractory symptoms.

The total doses of topical steroids used were calculated according to each group (class II– IV), grading the topical steroids[12] during the period of assessment.

Comparative study for assessing the efficacy of oral ApB

As a control, the clinical improvement of 55 patients with AD who were treated by conventional therapy, without oral ApB, was monitored over a 3 and 6 month period. Controls included 12 patients who showed lower compliance (< 25%) to therapy with oral ApB and other patients who did not receive ApB but who met the indications for oral ApB therapy.

Statistical analysis

The Kruskal–Wallis test, Mann–Whitney *U*-test, Wilcoxon signed-rank test, χ^2 test and unpaired *t*-test were used to test for significant differences.

RESULTS

CAP-RAST levels in subjects treated with oral ApB

Figure 1 shows the geometric means of CAP-RAST levels to *C. albicans* and *Df* and total serum IgE in three groups of ≤ 3, 4–6 and ≥ 7 according to the sum of CAP-RAST class to five food allergens, including egg, milk, soy bean, rice and wheat. Using the unpaired *t*-test, there were significant differences found among the mean CAP-RAST levels to *C. albicans* in the three groups. This suggests that in these subjects the sum of the CAP-RAST

class to the five food allergens was associated with CAP-RAST levels to *C. albicans*.

Efficacy of oral ApB on refractory symptoms

Table 2 shows the overall assessment of treatment response to oral ApB, evaluated according to the criteria described earlier. Symptoms that improved were dryness of the skin, erythema, severe itching, recurrent eczema and prurigo on the face and on other parts of the body. Times of assessment were expressed as mean days required for evaluating efficacy. The results of overall assessment were 'excellent' in 20% of subjects (25 of 125 patients) at 53.8±9.1 days, 'good' in 36.8% of subjects (46 of 125 patients) at 92.9 ±10.2 days, 'fair' in 16% of subjects (20 of 125 patients) at 94 ± 22 days and 'useless' in 27.2% of subjects (34 patients, including 11 patients deemed 'worse') at 94.3 ±12.4 days.

Laboratory characteristics according efficacy

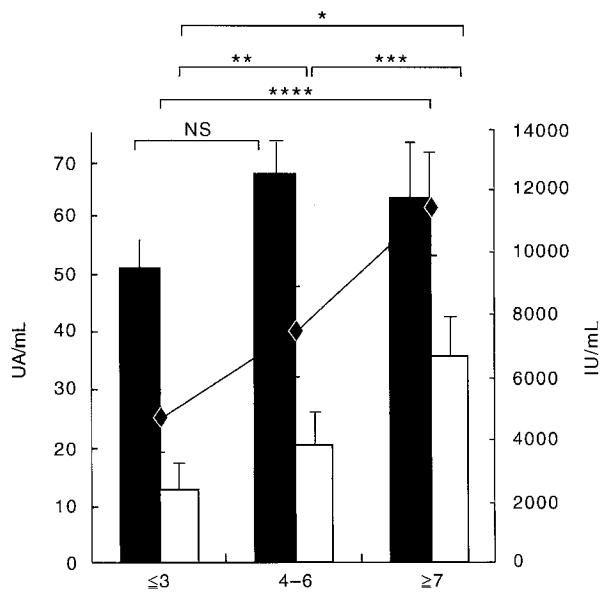
Statistical differences between clinical characteristics of subjects in whom treatment was assessed as excellent (group A), good (group B) and fair (group C) as well as those patients in whom treatment was assessed as useless (group D) were analyzed as shown in Table 3. There was no significant difference in the number of patients (%) with serum IgE levels ≥ 1000 IU/mL, the geometric mean of CAP-RAST levels to *C. albicans*, the number of patients (%) who were positive for *Candida* spp. in the stools and the sum (mean) of CAP-RAST class to food allergens. The number of patients (%) adhering to the restricted diet was significantly higher in group B than in group D ($P < 0.05$), while the geometric mean of CAP-RAST levels to *Df* was significantly higher in group D than in group B ($P < 0.05$).

Changes of laboratory data oral ApB

In patients in groups A, B and C (Table 3), it was determined that CAP-RAST levels of *C. albicans* were significantly lower after treatment with oral ApB compared with levels prior to treatment (12.3±3.8 and 17.9±3.5 UA/mL, respectively; $P < 0.01$). The geometric mean of IgE-radioimmunosorbent test (RIST) ($P < 0.01$), CAP-RAST levels to egg white ($P < 0.01$), soy bean ($P < 0.01$), rice ($P < 0.05$), wheat ($P < 0.01$) and LDH ($P < 0.01$)) were significantly lower after treatment with oral ApB than before treatment, as shown in Table 4.

Changes in doses of topical steroids used

The total doses of strong[12] topical steroids (class II or III) decreased with improvements in AD due to treatment with oral ApB, as shown in Fig. 2. The average quantity of class III topical steroids prescribed in the ApB group after ApB therapy (total: $n = 61$, 9.0 g/2 weeks; A: $n = 12$, 2.8 g/2 weeks) was significantly lower than that before treatment with ApB (total: $n = 48$, 19 g/2 weeks; A: $n = 9$, 12.4 g/2 weeks) and that in the control group ($n = 36$, 13.3 g/2 weeks; Fig. 2a). The number of patients with a decreased requirement for topical steroids was 91% of 21 patients using topical steroids in class II, 80% of 48 patients in class III and 66% of 43 patients in class IV (Fig. 2b). The mean percentage decrease in the quantity of topical steroids prescribed during treatment



IgE (*n*)	68	32	19
Df (*n*)	65	31	18
C. albicans (*n*)	68	33	19

Fig. 1 Geometric means of CAP-RAST levels (UA/mL) to *Candida albicans* (□) and *Dermatophagoides farinae* (*Df*; ■) and total serum IgE (IU/mL; –◆–) in ≤ 3, 4–6 and ≥ 7 of three groups according to the sum of CAP-RAST class to five representative food allergens, including egg white, cows' milk, soy bean, wheat and rice. Unpaired *t*-test: *P<0.001, **P<0.05, ***P<0.01, ****P<0.0001.

Table 2. Overall assessment of treatment response and days required for evaluating efficacy

	Efficacy*				
	Excellent	Good	Fair	Useless	Total
No. patients (%)	25 (20)	46 (36.8)	20 (16)	34 (27.2)	125 (100)
Mean (±SEM) days required for evaluating efficacy	53.8 (9.1)	92.9 (10.2)	94 (22)	94.3 (12.4)	84.5 (6.4)

*Efficacy: overall assessment was based on clinical improvement. Excellent, remarkable improvement for clinical symptoms; good, definite improvement; fair, slight but insufficient improvement; useless, no improvement or condition worsened.

Table 3. Characteristic background according to treatment response to oral amphotericin B

	Overall assessment of efficacy*				
Background	A	B	C	D	*P* value
Total serum IgE (IU/mL)					
Geometric mean±SEM	5973±1556	4506±714	8523±1774	8003±1664	0.2081‡
(No.)	(25)	(45)	(20)	(34)	
No. ≥ 1000 (%)	18 (19.5)	33 (35)	18 (19.1)	25 (26.4)	0.4638§
CAP-RAST (UA/mL; Geometric mean±SEM)					
Dermatophagoides farinae	120.8±38	85.1±20	251.3±112	239.8±80	0.6126‡**
(No.)	(22)	(45)	(18)	(33)	
Candida albicans	19.4±5	15±3.4	38.7±13	14.5±3.2	0.4290‡
(No.)	(25)	(45)	(20)	(32)	
No. positive candida spp. in the stools (%)	4 (21.1)	10 (52.6)	0 (0)	5 (26.3)	0.1334§
Sum of CAP-RAST class to food allergens† (mean±SEM)	3.2±0.6	2.8±0.4	3.4±0.7	2.1±0.5	0.2890‡
Practice of diet for responsive allergens					
No. patients (%)	15 (24.2)	25 (40.3)	8 (12.9)	14 (22.6)	0.3620§#

*A, excellent; B, good, C, fair; D, useless.
‡Kruskal-Wallis test; §χ^2 test. **B<D: $P<0.05$; #B>D: $P<0.05$.
†Egg white, cows' milk, soy bean, wheat, rice.

Table 4. Improvement of laboratory data in subjects who showed definite response to oral amphotericin B

		No.	Geometric mean (SEM)		Wilcoxon signed-rank*
IgE-RIST	(a)	40	4806.2	(755.6)	
(IU/mL)	(b)	32	3639.3	(673.9)	z=−2.844, #P=0.0045
CAP-RAST (UA/mL) levels to:					
Egg white	(a)	35	5.16	(3.1)	
	(b)	27	4.08	(2.5)	z=−2.792; #P=0.0052
Milk	(a)	29	0.99	(0.5)	
	(b)	24	0.77	(0.1)	z=0; P>0.9999
Soy bean	(a)	34	1.86	(0.5)	
	(b)	27	1.03	(0.3)	z=−3.139; #P=0.0017
Rice	(a)	37	2.73	(0.8)	
	(b)	27	1.28	(0.3)	z=−2.005; #P=0.045
Wheat	(a)	37	3.46	(0.9)	
	(b)	26	2.15	(0.6)	z=−3.1; #P=0.0019
Dermatophagoides farinae	(a)	36	49.11	(6.4)	
	(b)	29	58.96	(7.5)	z=−1.799; P=0.072
Candida albicans	(a)	39	17.9	(3.5)	
	(b	29	12.30	(3.8)	z=−2.877; #P=0.004
Lactate dehydrogenase (IU/L)	(a)	32	531	(38)	
	(b)	30	427	(26)	z=−3.541; #P=0.0004

(a), At the time oral amphotericin B (ApB) was started; (b), 6 months to 1 year after oral ApB was started.
*Statistical difference between (a) and (b). #P value significantly different.

with ApB compared with that prescribed prior to treatment was 57.4±13.9 in class II ($n = 21$), 35.3±11 in class III ($n = 48$) and 18.0±10.2 in class IV ($n = 43$; Fig. 2c).

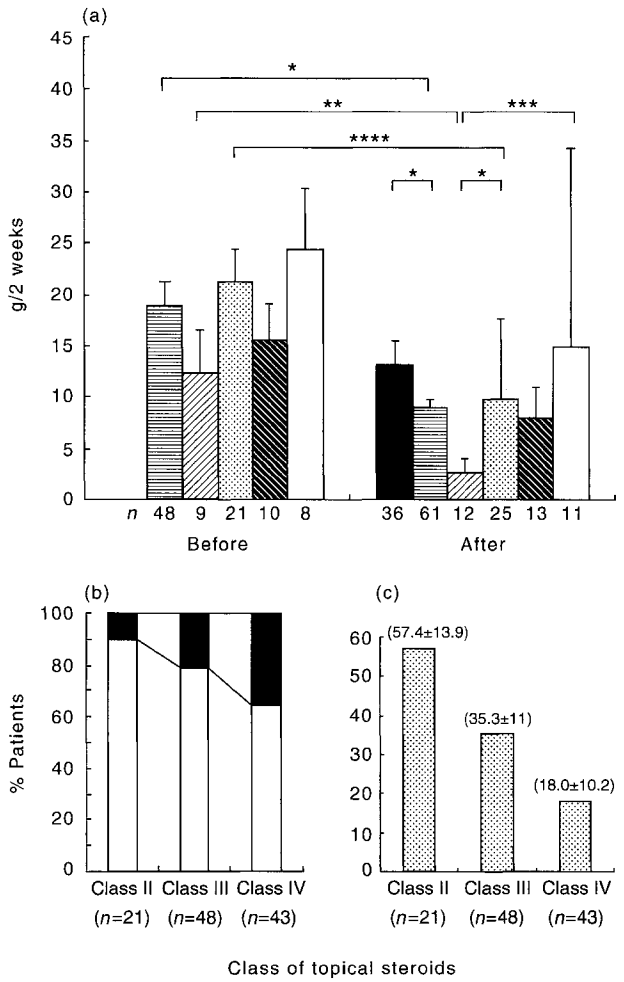


Fig. 2 Changes in the quantity and quality of topical steroids prescribed during treatment with oral amphotericin B (ApB). The use of topical steroids was estimated by doses prescribed before treatment with ApB (Before) and during the final assessment of overall improvement (After). (a) Average quantity of class III topical steroids, prescribed in the ApB group: total ApB (▤), A (▨), B (▩), C (▧) and D (□) group according to efficacy and the control group (■). The data are expressed as mean quantity (±SEM) g/2 weeks of topical steroids prescribed. (b) The ratio of patients with a decrease in topical steroids (□) compared with those patients with an increase in topical steroids (■) during the final evaluation of the efficacy of ApB in comparison with the quantity required before treatment with ApB. (c) The mean percentage of the decrease in the quantity of steroids prescribed during treatment with ApB compared with that prescribed before treatment.

Comparative study in controls not treated with oral ApB

The pretreatment characteristics of the 125 patients receiving oral ApB were compared with pretreatment characteristics of 55 patients who did not receive ApB. There were no significant differences in age, gender, duration or severity of AD, type of eruptions, or adherence to dietary restrictions for food allergens between these two patient groups, as shown in Table 1. Laboratory evaluations of total serum IgE, CAP-RAST levels to *C. albicans* and the sum of positive CAP-RAST class to each food allergen also showed no significant differences between the patient groups (Table 1). With regard to the improvement of symptoms with oral ApB treatment, the percentage of patients treated with ApB who showed 'definite improvement' or 'remarkable improvement' was 16.8 and 53.6%, respectively, of 125 cases over a 3 month period and 35.2 and 47.9%, respectively, of 71 cases over a 6 month period; this was significantly higher ($P < 0.01$) than the 1.8 and 36.4%, respectively, of 55 controls over a 3 month period and 8.3 and 36.1%, respectively, of 36 controls over a 6 month period, as shown in Fig. 3.

Side effects of oral ApB for AD

Gastrointestinal symptoms, such as nausea ($n = 1$), diarrhea ($n = 1$) and abdominal pain ($n = 1$), and aggravation of pruritus ($n = 2$) were observed in a few patients (5/125; 4%). There were no laboratory abnormalities over a 6 month observation period.

Discussion

The present study assessed anti-*Candida* therapy using oral ApB in treating recalcitrant AD that failed to respond to standard treatment. Efficacy was 'excellent' or 'good' in 56.8% of 125 patients, 'fair' in 16% of patients and 'useless' in 27.2% of patients. This assessment was better than the overall efficacy of oral Ny, general efficacy which showed a rate of 49% in previous studies.[7] Clinically recalcitrant lesions, including facial erythema and recurrent lesions refractory to topical steroids, were improved by ApB in subjects showing excellent or good efficacy. The mechanism by which oral ApB improved such refractory symptoms remains unknown. In a previous study[13] we have shown that serum CAP-RAST–IgE levels to *C. albicans* increase depending on the severity of AD. The *Candida* spp. are mainly resident flora

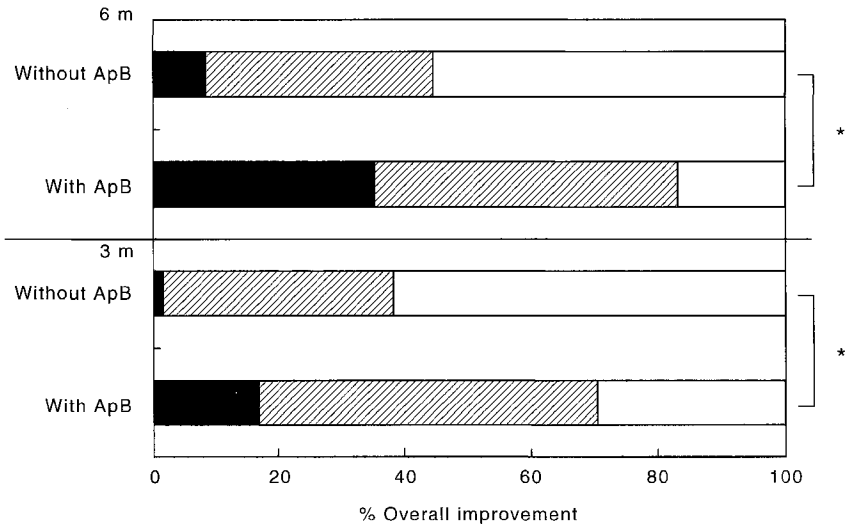


Fig. 3 Improvement was assessed 3 and 6 months (m) after oral amphotericin B (ApB) had started as no change or worse (□), definite improvement (▨) or remarkable improvement (■). *$P<0.01$ (Mann–Whitney *U*-test).

	3 months		6 months	
Assessment	With ApB	Without ApB	With ApB	Without ApB
Remarkable improvement (%)	16.8	1.8	35.2	8.3
Definite improvement (%)	53.6	36.4	47.9	36.1
No change or worse (%)	29.6	61.8	16.9	55.6
Total no. patients	125	55	71	36

in vivo, although *Candida* spp. are also environmental fungi. Tanaka *et al.*[14] demonstrated IgE-mediated hypersensitivity and contact sensitivity to a crude extract of C. *albicans* in patients with AD and also demonstrated a lower frequency of positivity on patch tests to C. *albicans* with simultaneously higher levels of RAST to C. *albicans* in the same group of patients. Those authors supposed that persistence of C. *albicans* in the digestive tract may induce a Th2-type T cell response. Savolainen *et al.*[15] described that specific IgE to C. *albicans* increased and delayed hypersensitivity to C. *albicans* decreased in severe types of AD. It is suggested that unbalanced Th1/Th2 reactivity in AD patients is able to help saprophytic growth of those *Candida* spp. and to get patients with AD sensitized to antigens of these *Candida* spp. From this perspective, treatment of saprophytic *Candida* spp. in AD is needed to enable those patients to recover from refractory AD. Actually, in the present study, oral anti-*Candida* therapy helps symptoms to wane and reduces IgE specific to *Candida*. Oral anti-*Candida* therapy may reduce cross-reactive antibodies to *Pityrosporum ovale/orbiculare*, which are resident flora on the face, and this may also help to improve facial inflammation.[17,18] According to the grade of efficacy, there were no significant differences in CAP-RAST levels to C. *albicans*, the prevalence of *Candida* spp. in the stools or the sum of CAP-RAST class to food allergens in subjects in the present study. However, adherence to restrictions imposed for food allergy affected the efficacy of oral ApB, although the reason for this remains unclear. In our experience, orally administered ApB tablets show a greater efficacy than does ApB syrup (data not shown). As the ApB tablet mainly targets fungi in the lower digestive tract in comparison with ApB syrup, we suppose that oral ApB targets *Candida* in the lower digestive tract. As the sum of the positive class of CAP-RAST to food allergens increased, CAP-RAST levels to *Candida* also increased. There were significant differences between pretreatment laboratory data, including mean CAP-RAST levels to food allergens, and data obtained 1 year or 6 months after treatment with ApB. Pretreatment CAP-RAST levels of C. *albicans* tended to be higher than those after treatment, but CAP-RAST levels to *Df* did not show any change after treatment. The laboratory diagnosis of overgrowth of *Candida* spp. and hypersensitivity to *Candida* in the digestive tract or yeast connection are not yet proven. However, based on the CAP-RAST data and on the clinical response to oral ApB tablets, intestinal *Candida*

spp. or allergic reactions to *Candida* spp. in the intestine seem likely to increase the passage of food allergens through the intestinal wall. These data indicate that *Candida* in the digestive tract acts as an allergen carrier, helping food allergies to persist. Therefore, the oral administration of anti-*Candida* therapy along with the control of exposure to food allergens is necessary in recalcitrant AD accompanied by food allergy.

Furthermore, we recommended that patients receiving anti-*Candida* therapy follow a low yeast diet, as *Candida* are known to share some epitopes with *Saccharomyces cerevisiae*.[16,18] However, it remains unknown whether *S. cerevisiae*, *Aspergillus orysae*, *Saccharomyces rouxii* and *Lactobacillus casei*, which are consumed with foods including bread, alcoholic beverages, soy sauce, miso and cheese, cause patients to become sensitized to *Candida* spp., thus aggravating or facilitating the persistence of AD in patients sensitized to *Candida*.

Efficacy of oral ApB was assessed after 3 and 6 months.Better results were obtained earlier than were worse results. We assume that observations over periods longer than 3 months without signs of improvement are not useful in the evaluation of the efficacy of oral ApB on AD.

Other evidence of ApB efficacy included serum total IgE, LDH[11] and the fact that both doses and gradings of the topical steroids used decreased in subjects showing significant improvement within 1 year or 6 months after oral ApB commenced. Although the frequency of recurrence of AD after discontinuing oral ApB was not examined in the present study, we did encounter some patients showing recurrent AD symptoms after discontinuing oral ApB. We would like to examine the prevalence of recurrence in subjects treated by oral ApB in the next study. The results obtained in patients using oral ApB demonstrated significant effectiveness of the treatment compared with results from controls. However, we must be cautious in interpreting the results of the present study, as 27.2% of patients receiving oral ApB did not respond to therapy. These patients had significantly higher IgE to *Df*. Therefore, environmental allergens would have to be more strictly controlled in these patients. As ApB is hardly absorbed through the gastrointestinal tract,[19] when *Candida* infection becomes invasive, ApB does not affect the invasive lesions of intestinal candidiasis. Triazoles, such as fluconazole and itraconazole, may be suitable for such cases.[4]

As indicated earlier, while aggravated or refractory AD appeared in patients who had high levels of specific IgE to *C. albicans* and food, the link with candidiasis in the digestive tract is by association rather than by direct evidence. Mudde *et al.*[20] showed that, in AD, epidermal Langerhans cells (LC) not bearing IgE present *Candida* allergens as do LC bearing IgE. Therefore, to examine levels of specific IgE to *C. albicans* is not enough to suggest an allergic reaction to *Candida* allergens in AD. Concerning the detection of the saprophytic growth of *Candida* spp., Buslau *et al.*[21] have reported that yeasts were detected in stool samples from 70% of AD patients. The results of the present study did not show any difference in the prevalence of *Candida* spp. cultured from the feces of patients with AD compared with healthy subjects. In trials of serodiagnosis of *Candida* spp. overgrowth in the digestive system, D-arabinitol, an enzyme secreted from *Candida* spp., or β-D-glucan, a cell wall component of *Candida* spp., in sera are supposed to be available for some patients.[22] However, as AD patients are not compromised hosts but have a diseased state, D-arabinitol or β-D-glucan are not reliable indicators in all cases. Other methods of serodiagnosis for intestinal candidiasis are expected to be developed.

REFERENCES

1 Matsuda M, Takahashi M. Nystatin-therapy for atopic dermatitis. Intestinal candidosis as pathogenic microflora in atopic dermatitis. *Arerugi no rinsyo (The Allergy in Practice)* 1991; **11**: 768–72 (in Japanese).

2 Komura A, Hanagaki H, Adachi A, Takashima T, Horikawa T. Influence of candida antigen on atopic dermatitis. *Jpn. J. Dermatoallergol.* 1993; **1**: 217–22.

3 Inoue N, Kamiide R. Treatment for facial eruptions in atopic dermatitis. *JJOCD* 1994; **40**: 52–5.

4 Fujita H, Ogusu K, Imaizumi T. Experience in treating adult-type-atopic dermatitis with high CAP-RAST levels to *C. albicans* with antifungal drug. *Acta. Dermatol.* 1995; **90**: 461–3.

5 Thomas I. Superficial and deep candidosis. *Int. J. Dermatol.* 1993; **32**: 778–83.

6 James J, Warin RP. An assessment of the role of *Candida albicans* and food yeasts in chronic urticaria. *Br. J. Dermatol.* 1971; **84**: 227–37.

7 Suga C, Miyakawa K, Sugiyama A, Komatsu T, Takahashi K, Ikezawa Z. Efficacy of antifungal therapy on atopic dermatitis. *Jpn. J. Allergol.* 1992; **41**: 338.

8 Iwata K. Polyene antibiotics. In: *Fungi, fungal infections and chemotherapy, focus on antifungal agents.* Tokyo: Soft Science Publications, 1994; 169–74.

9 Tagami H. Japanese dermatological association criteria for the diagnosis of atopic dermatitis. *Jpn. J. Dermatol.* 1996; **106**: 64–5.
10 Miyakawa K, Hirai Y, Miyakawa J *et al.* Statistical analyses of the diagnostic criteria, clinical severity, IgE-RAST score, and serum IgE value in the patients with atopic dermatitis (AD): Probable involvement of the food antigens, especially of the rice, in the severe patients. *Allergy* 1988; **37**: 1101–10.
11 Mukai H, Noguchi T, Kamimura K, Nishioka K, Nishiyama S. Significance of elavated serum LDH (lactate dehydrogenase) activity in atopic dermatitis. *J. Dermatol.* 1990; **17**: 477–81.
12 Aso M, Shimamura S, Iwasaki K *et al.* A study on suppression of adrenocortical function by percutaneous absorption of topical steroids. *Nishi Nihon J. Dermatol.* 1989; **51**: 352–8 (in Japanese).
13 Ikezawa Z, Kitamura K. Atopic dermatitis and fungus- or bacterial allergy. *Arerugi no rinsyo (The Allergy in Practice)* 1995; **15**: 25–9.
14 Tanaka M, Aiba S, Matsumura N, Aoyama H *et al.* IgE-mediated hypersensitivity and contact sensitivity to multiple environmental allergens in atopic dermatitis. *Arch. Dermatol.* 1994; **130**: 1393–401.
15 Savolainen J, Koivikko A, Kalimo K *et al.* IgE, IgA and IgG antibodies and delayed skin response towards *Candida albicans* antigens in atopics with and without saprophytic growth. *Clin. Exp. Allergy* 1990; **20**: 549–54.
16 Koivikko A, Kalimo K, Nieminen E, Savolainen J, Viljanen M, Viander M. Allergenic cross-reactivity of yeasts. *Allergy* 1988; **43**: 192–200.
17 Jarolim EJ, Poulsen LK, With H, Kieffer M, Ottevanger V, Skov PS. Atopic dermatitis of the face, scalp, and neck: Type I reaction to the yeast *Pityrosporum ovale*? *J. Allergy Clin. Immunol.* 1992; **89**: 44–51.
18 Ito K, Sakamono T, Kikuchi S *et al.* Detection of IgE antibody to *Pityrosporum orbiculare* in patients with atopic dermatitis. *Jpn. J. Allergol.* 1995; **44**: 481–90.
19 Tomiyama, T. A study of absorption and excretion of amphotericin B (I). The concentration of amphotericin B in the serum and organs, following oral administration for long periods. *Jpn. Pharmacol. Ther.* 1975; **3**: 63–71.
20 Mudde GC, van Reijsen FC, Boland GJ, de Gast GC, Bruijnzeel PLB, Bruijnzeel-Koomen CAFM. Allergen presentation by epidermal Langerhans cells from patients with atopic dermatitis is mediated by IgE. *Immunology* 1990; **69**: 335–41.
21 Buslau M, Menzel I, Holzman H. Fungal flora of human faeces in psoriasis and atopic dermatitis. *Mycoses* 1990; **33**: 90–4.
22 Marufuji T, Kuwabara H, Sumiya T, Tedo I. Pitfalls in the diagnosis of systemic fungal infections using newly developed serological tests β-D-glucan and D-arabinitol. *Jpn. J. Intens. Care Med.* 1991; **15**: 279–84.