

Is topical antimycotic treatment useful as adjuvant therapy for flexural atopic dermatitis: randomized, double-blind, controlled trial using one side of the elbow or knee as a control

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Abstract

Background Certain factors are known to cause exacerbation of atopic dermatitis (AD), e.g. soap, detergent, dry skin, staphylococcal colonization, and herpes infection. Other factors are suspected, but not yet proven, e.g. yeasts belonging to the *Malassezia* genus. It is known that antimycotics may be beneficial in a small subset of adult patients with dermatitis affecting the head and neck region; however, it is not known whether AD patients, many of whom also have head and neck involvement, may also find antimycotics useful. A previous study has demonstrated no treatment difference in adult AD patients; however, the measurement method was criticized and 1% hydrocortisone cream may have too weak an effect in adult patients. Therefore, we designed this randomized, double-blind, controlled trial to examine this question. Younger AD patients were recruited and different methods of measuring outcomes were used. **Objective** To evaluate the usefulness of topical antimycotic treatment as adjuvant therapy for flexural AD.

Methods This was a randomized, double-blind, controlled trial in AD patients using one side of the elbow or knee as a control. There were three independent outcomes: (i) to compare the ability to relieve symptoms; (ii) to compare the ability to improve clinical signs; and (iii) to compare the ability to provide lasting clinical effects.

Results All three outcomes showed unequivocally that the addition of antimycotic did not provide extra benefit to the standard treatment.

Conclusion The addition of antimycotic does not seem to provide extra benefit to AD patients, and the beneficial effect of this medication seems to be restricted to a small subset of adult patients with dermatitis affecting the head and neck region.

Background information and rationale

Atopic dermatitis (AD) is a chronic, relapsing, itchy, inflammatory skin condition usually starting from childhood.¹ Only around one-third of AD patients suffer from skin problems alone according to a Singapore study;² the remaining patients often also suffer from other atopic conditions, such as rhinitis, asthma, and hay fever. Certain factors are known to cause exacerbation in AD, e.g. soap, detergent, dry skin, staphylococcal colonization, and herpes infection.³ Other factors are suspected, but not proven, e.g. yeasts belonging to the *Malassezia* genus.⁴

Malassezia yeasts are considered to be part of the normal skin flora, and are capable of inducing both immunoglobulin

E (IgE)-mediated^{5,6} and T-cell-mediated⁷ immune responses in AD patients. These immune responses may cause the inflammation of skin in AD.⁴ In atopic patients, *Malassezia*-specific IgE is detectable in atopy with skin involvement only, but rarely in other forms of atopy.⁸ In atopic patients with skin involvement only, the positive prevalence rate of *Malassezia*-specific IgE is higher in those with head and neck involvement only than in those with other sites of involvement.⁹

Although AD patients often have elevated serum IgE to a wide range of allergens, the significance of this observation for the pathogenesis of AD has remained unclear.¹⁰ Therefore, the value of using *Malassezia*-specific IgE prevalence as pathophysiologic evidence in AD also remains unclear. Furthermore, the currently accepted species of *Malassezia* have

increased from seven in 2003¹¹ to 11 in 2005.¹² Therefore, it is difficult for commercially manufactured radioallergosorbent (RAST) and skin prick (SPT) tests to keep abreast of these changes. In addition, it is difficult to interpret previous *Malassezia*-specific IgE measurements, as there are bound to be many false negatives.

Randomized controlled trials that have tested the usefulness of antifungal medication in AD, in either oral or topical form, are sparse. Oral ketoconazole, 200 mg daily, appeared to be better than placebo ($P < 0.005$) in a group of *Malassezia* SPT-positive dermatitis patients with mainly head and neck involvement.¹³ However, no significant difference was found when the same medication was given to a group of AD patients with head and neck involvement. These two studies were similar, except that the patients in the latter study were restricted to AD and the affected areas were more generalized.¹⁴ Only one randomized controlled trial has tested topical antifungal medication in a group of AD patients with head and neck involvement. The difference in severity scores did not reach statistical significance when antifungal medication was added to the standard treatment (hydrocortisone).¹⁵ The question of the appropriateness of using SCORing Atopic Dermatitis (SCORAD) as the measurement tool in this rather localized form of AD was raised.⁴ Indeed, for *Malassezia* species to play any role at all in the exacerbation of AD, trials need to demonstrate better treatment outcomes, including both symptoms and signs, when antimycotics are added to standard treatments. Moreover, the clinical effect of the antimycotic group should last longer than that of the standard group. Therefore, we designed this randomized controlled trial to evaluate the effect of the addition of antimycotic on different clinical outcomes, i.e. symptoms, signs, and time to relapse. Moreover, the ages of the patients were restricted to 5–14 years because, above this range, the effect of 1% hydrocortisone may be too mild, affecting the ability of this trial to evaluate the clinical effect of the antimycotic.

Methods

Patients

Thirty AD patients were recruited between August 2005 and March 2006 from the Outpatient Pediatric Department, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China. In order to qualify as a case, an individual had to fulfill the UK Working Party's Diagnostic Criteria for Atopic Dermatitis.¹⁶ Furthermore, all patients were aged between 5 and 14 years, and had active disease evenly affecting the knees or elbows. In addition, patients were asked whether they had used any form of antimycotic in the last 3 months.

Study design

This 2-week, randomized, double-blind, placebo-controlled study was conducted at the Outpatient Pediatric Department, Chinese

University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China. The Ethics Committee of the Prince of Wales Hospital approved the protocol. Patients who met the entry criteria and their parents/guardians, when applicable, gave their written informed consent before the study procedures. Dakacort hydrocortisone cream was supplied without any financial support from Janssen Pharmaceutical.

Study medication and blinding

There were 30 consecutive envelopes, each containing two bottles of cream, one labeled right and the other left. One side of the patient's elbow or knee was randomized to receive 1% hydrocortisone plus miconazole cream and the other to receive 1% hydrocortisone cream. Patients were particularly reminded to use different applicators for the different sides, otherwise the result would be affected. The patients, investigator, and dermatologists were blind to which side received which treatment.

The study medication was applied twice daily, approximately 12 h apart, to the affected areas throughout the entire treatment period of 2 weeks. No concomitant topical medication was allowed, except for the usual cleansers and moisturizers.

Assessments

Three independent outcomes were used to evaluate the efficacy of antimycotic as adjuvant therapy for flexural AD.

The first outcome evaluated the ability to relieve symptoms and the presence of possible side-effects. Patients were asked three questions after 2 weeks of treatment: (i) had they finished the treatment?; (ii) had they noticed any side-effects?; and (iii) had they noticed any difference between the two sides?

The second outcome evaluated the ability to improve the clinical signs. Clinical photographs were taken before and after 2 weeks of treatment; an example is shown in Figs 1 and 2. Two dermatologists were asked separately to compare any differences.



Figure 1 Patient 17 before treatment



Figure 2 Patient 17 after 2 weeks of treatment

The third outcome evaluated the ability to provide lasting clinical effects. At the end of 2 weeks, all active treatments were stopped, except moisturizers, and the patients were then followed up for a further 6 weeks. During this period, the number of days for each side for which patients did not require steroid cream for symptomatic relief was recorded, and the difference for each patient was noted for analysis.

Statistical analysis

Descriptive statistics are provided for background and demographic characteristics, severity of disease, distribution of involvement, possible side-effects, and the dropout rate.

The first outcome was recorded at the end of 2 weeks. McNemar's test was used to check for any discordant pair, i.e. any statistical difference between the side receiving 1% hydrocortisone plus miconazole cream and the side choosing 1% hydrocortisone cream only in terms of symptomatic relief judged by the patients.

The second outcome used McNemar's test to check for any discordant pair with regard to differences in the clinical signs judged by two dermatologists by looking at the pre- and post-treatment photographs. Further statistical analysis using Cohen's κ checked the reproducibility of this method between the two dermatologists.

In the third outcome, all patients were followed for a further 6 weeks to investigate the number of days for each side for which patients did not require steroid cream for symptomatic relief. The Wilcoxon signed rank test was used to check for any statistical difference between the two treatments.

Lehr's formula¹⁷ was used to calculate the sample size for a power of 80% and a two-sided significance level of 0.05. To be clinically significant, eight of 10 patients would prefer antimycotic, giving a standardized difference of $0.8 - 0.2 = 0.6$; therefore, the total number of patients required was $16/0.6^2 = 44.4$. As patients were using one side as a control, 23 patients were required. As

some patients might show no difference at all, it was decided that 30 patients would be recruited.

Results

Thirty patients were enrolled and only one patient was lost to follow-up. The baseline demographics and disease characteristics are given in Table 1. There were more male than female patients. Over 80% of patients had severe disease with head and neck involvement.

The first outcome was measured 2 weeks after the start of the study. Twenty-nine patients completed the treatment and none complained of side-effects. There was a similar preference between the two groups (Table 2).

Table 1 Demographic characteristics

Gender, <i>n</i> (%)		
Male	20	(67)
Female	10	(33)
Associated with other atopies, <i>n</i> (%)		
Yes	18	(60)
No	12	(40)
Disease on scalp, <i>n</i> (%)		
Yes	12	(40)
No	18	(60)
Disease on head/neck, <i>n</i> (%)		
Yes	25	(83)
No	5	(17)
Disease on elbow/knee/ankle, <i>n</i> (%)		
Yes	28	(93)
No	2	(7)
Disease on upper limbs, <i>n</i> (%)		
Yes	23	(77)
No	7	(23)
Disease on lower limbs, <i>n</i> (%)		
Yes	24	(80)
No	6	(20)
Disease on trunk, <i>n</i> (%)		
Yes	14	(47)
No	16	(53)
Nottingham eczema severity score, <i>n</i> (%)		
Mild	2	(7)
Moderate	4	(13)
Severe	24	(80)
Age (years)		
Mean	10.3	
SD	2.6	
Range	5–14	
Duration of disease (months)		
Mean	73.9	
SD	50.1	
Range	4–162	
Age at onset (months)		
Mean	19.6	
SD	21.4	
Range	2–96	

Table 2 Patient outcome

Outcome	No. of patients	P*
Better response with antimycotic + hydrocortisone	10	0.424
Better response with hydrocortisone only	15	
No difference	4	

*McNemar test.

Table 3 Dr A's outcomes

Outcome	No. of patients	P*
Better response with antimycotic + hydrocortisone	10	0.999
Better response with hydrocortisone only	9	
No difference	10	

*McNemar test.

Table 4 Dr B's outcomes

Outcome	No. of patients	P*
Better response with antimycotic + hydrocortisone	2	0.999
Better response with hydrocortisone only	1	
No difference	26	

*McNemar test.

For the second outcome, two dermatologists (Dr A and Dr B) were invited to examine the before- and after-treatment photographs of the 29 patients. Both were unable to distinguish statistically between the two treatments (Tables 3 and 4). The preferences for each patient are shown in Table 5, and Cohen's κ value was 0.059.

For the third outcome, around 80% of patients restarted treatment of both sides simultaneously; for the remaining 20%, both types of treatment provided similar clinical effects (Table 6).

Discussion

Although some authors believe that antifungal treatment may be useful in most AD patients with head and neck involvement,⁴ others take a more conservative approach and believe that the benefit is only restricted to a small subset of adult AD patients with head and neck involvement.¹⁸ This clinical trial was designed to help us answer the following question: do young AD patients find antimycotic treatment useful? Furthermore, flexural AD patients were selected because a very high proportion have head and neck involvement, which

Table 5 Dr A and Dr B's assessments on clinical photographs

Patient	Dr A*	Dr B*
1	1	3
2	3	3
3	2	3
4	1	4
5	2	3
6	Missing	Missing
7	2	1
8	2	2
9	2	3
10	2	3
11	1	1
12	2	3
13	2	4
14	3	4
15	2	3
16	4	4
17	3	3
18	2	3
19	3	3
20	1	4
21	2	3
22	3	4
23	2	3
24	2	3
25	3	3
26	3	4
27	3	3
28	3	4
29	2	3
30	1	3

*Doctor's assessment on clinical photographs: 1, right side better; 2, left side better; 3, both sides better; 4, both sides worse. $\kappa = 0.05$.

Table 6 Difference in days

Patient	Difference in days (antimycotic + hydrocortisone – hydrocortisone only)	P (Wilcoxon signed rank test)
2	2	0.528
5	–1	
13	–7	
17	21	
18	–18	
20	–21	

26 patients found no difference.

may be used as a surrogate marker for the presence of *Malassezia* yeasts.

All patients but one completed the study, and none complained of any side-effects. The result of the first outcome suggested that the addition of antimycotic did not seem to

provide any additional benefit from the patients' point of view. In the second outcome, when the pre- and post-treatment photographs were presented to the dermatologists, the results suggested that neither found the antimycotic more effective than the standard treatment, although the results from the two dermatologists were poorly correlated. In the third outcome, after observing the patients for a further 6 weeks, the addition of antimycotic did not seem to provide a more lasting clinical effect than standard treatment alone.

Therefore, it can be concluded from the results of the three different outcomes that it is highly unlikely that the addition of antimycotic will provide any beneficial effects to young AD patients with flexural involvement. These results are consistent with a previously reported randomized controlled trial in a similar group of patients, although the outcomes measured were different¹⁵; the use of different outcome methods to answer similar questions in different trials makes this conclusion more significant.

This trial could have been improved in a number of areas. Firstly, although the use of one side of the elbow or knee as a control avoids biological variability between individuals, and both sides are symmetrically affected, they are not necessarily affected to a similar degree; hence, their responses to treatment may be different. Therefore, the selection of the right patients for comparison would reduce bias from different treatment responses. Secondly, simple comparison of pre- and post-treatment photographs does not seem to be a reliable way to make a diagnosis, as shown by the low κ value, as photographs only provide two-dimensional images. If resources were available, it would be better to ask two dermatologists to make their separate diagnoses immediately after examining the patients; this would improve the accuracy of this test. Finally, patients should be given four options during randomization: both sides standard, both sides antimycotic, right antimycotic and left standard, or vice versa. Only two options were used in this study. This would prevent information bias arising from patients, who may believe that one side must be better than the other.

In conclusion, in this randomized, double-blind, controlled trial in a group of AD patients (age range, 5–14 years), using one side of the elbow or knee as a control, we found no evidence to suggest that topical antimycotic treatment is useful as an adjuvant therapy for flexural AD. As this conclusion has also been reached in an older group of AD patients using SCORAD as the outcome measure,¹⁵ it is probable that this beneficial effect applies only to a small subset of adult patients with dermatitis affecting the head and neck region. Whether this subset has any relationship with atopy is not certain.

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