

# The Circadian Rhythm of Itching among 241 Adults with Atopic Dermatitis: A Cross-sectional Study

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**The pattern of itching in patients with atopic dermatitis has not been systematically studied. Therefore, this study aimed to assess the pattern of itching in adults with atopic dermatitis using questionnaires to assess for a circadian rhythm of itching in participating patients at a single institution ( $n=241$ ). A self-report questionnaire was used to assess circadian rhythm and intensity of itching in patients. In addition, the patients' disease severity (Eczema Area and Severity Index [EASI]) and quality of life (Dermatology Life Quality Index [DLQI]) were assessed. Itching occurred most frequently (74.69%) and with the greatest severity (62.66%) between 20:00 and 00:00, and the least number of patients (25.31%) experienced itching between 04:00 and 08:00. The DLQI and EASI scores both correlated with the average and maximum itch intensity ( $r=0.582$ ,  $r=0.533$ , respectively;  $r=0.539$ ,  $r=0.517$ , respectively;  $p<0.001$ ). The DLQI and EASI scores were associated with average itch intensity ( $B=0.179$ ,  $B=0.204$ , respectively; 95% CI: 0.112 to 0.246, 95% CI: 0.096 to 0.313, respectively;  $p<0.001$ ), and the EASI score was associated with males and family history ( $B=0.285$ ,  $B=0.287$ , respectively; 95% CI: 0.094 to 0.476, 95% CI: 0.096 to 0.478, respectively;  $p=0.003$ ). Adult patients with atopic dermatitis exhibited a circadian rhythm of itching; these study results could positively impact treatment approaches.**

*Key words:* atopic dermatitis; circadian rhythm; itch; questionnaire.

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Atopic dermatitis (AD) is a non-fatal dermatosis with the highest global disease burden and is characterized by dry skin and intense itching (1). According to an international time-trend survey of the incidence and prevalence of AD, the prevalence ranges from 2% to 17.6% (2). Itching is not only the most important and typical symptom of AD but is also a contributing factor in the exacerbation and recurrence of AD (3, 4). Itching

## SIGNIFICANCE

This study systematically and comprehensively describes the circadian rhythm characteristics of itching in 241 adult patients with atopic dermatitis. Itch in adult patients with atopic dermatitis occurred most frequently and with the greatest severity between 20:00 and 00:00, and the least number of patients experienced itching between 04:00 and 08:00. This study lays a foundation for further research on the occurrence and regulatory mechanisms of itching, and also provides a basis for chronotherapy (which may enhance treatment efficacy and mitigate medication-related side effects).

often worsens at night, which not only seriously affects the physical and mental health of patients, but also may aggravate the disease (1, 5). Therefore, controlling nocturnal itching is of great significance in breaking the itch-scratch cycle and alleviating AD. Elucidating the circadian rhythm and specific characteristics of itching is important information for the development of treatments to manage AD.

Circadian rhythms are biological rhythms expressed in physiological or biological behaviours in cycles of approximately 24 h (6). These rhythms also play a role in influencing both normal and pathological processes within the skin, including temperature regulation, blood flow, transdermal water loss, and even itching (7–10). Previous studies have shown that itching is worse at night in individuals with AD (11, 12); however, the 24-h circadian rhythms of itching in adults with AD have not been systematically studied.

Chronotherapy is a therapeutic approach that aligns medication administration with circadian rhythms to enhance treatment efficacy and mitigate side effects (13, 14). Yoshioka et al. (15) conducted a study which revealed that nocturnal application of topical corticosteroids led to improved management of psoriasis plaques. This finding highlights the potential benefits of chronotherapeutic strategies for dermatological treatment. Defining the circadian rhythm of itching in patients with AD may elucidate the mechanisms of itch modulation and lead to targeted temporal therapies for managing itching. Therefore, this study aimed to investigate circadian rhythm patterns of itching in adult patients with AD using a cross-sectional questionnaire.

## MATERIALS AND METHODS

### Study design and participants

A total of 252 questionnaires were collected from patients by convenience sampling at the Third Xiangya Hospital of Central South University, Changsha, China, between September 2021 and October 2023. The response rate was 100%, with a valid questionnaire response rate of 95.63% (241/252). The researchers provided guidance and explanations for patients who had problems completing the questionnaires. The questionnaires were collected anonymously. Finally, a total of 241 patients aged 18–87 years completed the questionnaire. The inclusion criteria were as follows: (i) adult patients (18 years or older), (ii) patients who met the Hanifin–Rajka criteria (16) for the clinical diagnosis of AD, and (iii) patients in whom this was the first dermatological appointment. The exclusion criteria were as follows: (i) recent sleep disorders, irregular eating habits, or sleeping with lights on at night, as these factors can lead to circadian rhythm disruption; (ii) serious physical or mental illnesses that prevented cooperation with the researcher; and (iii) other conditions that could cause itching. This study was approved by the hospital ethics committee (approval number: Fast 23345). Written informed consent was obtained from each participant before any study-related procedures were performed.

### Itch questionnaire

All participants were asked to complete a self-report questionnaire that has 5 questions on itch circadian rhythm and intensity (Fig. S1). The self-report questionnaire was developed by 9 experienced experts in our research group and revised in the clinic after 2 months of pre-experiment. Before assessing the circadian rhythm and intensity of itching, patients were asked whether the intensity of itching was the same throughout the day. If the patient reported variations in itch intensity across different times of the day, they were prompted to continue to the next question. Conversely, if the intensity was reported as consistent, the questionnaire was terminated. As to circadian rhythm of itching, we divided 24 h of the day into 6 time periods (00:00–04:00, 04:00–08:00, 08:00–12:00, 12:00–16:00, 16:00–20:00, and 20:00–00:00) (17, 18). The patients selected the time periods of a day when the itching occurred and when the worst itching occurred (multiple choice). To quantify the average itch intensity and the maximum itch intensity of the patient during a day, an 11-point numeric rating scale (NRS) was employed, with 0 representing “no itch” and 10 indicating “the worst imaginable itch”. Patients choose the scores in NRS respectively for the average itch intensity and the maximum itch intensity of a day (multiple choice).

### Eczema Area and Severity Index

The Eczema Area and Severity Index (EASI) provides a comprehensive assessment of the head and neck (H), upper limbs (UL), trunk (T), and lower limbs (LL). Four body regions are assigned a score based on the percentage of the area involved (A): 0 (no eruption), 1 (0–9%), 2 (10–29%), 3 (30–49%), 4 (50–69%), 5 (70–89%), and 6 (90–100%). The 4 body regions are also assessed for erythema (E), induration/population (I), excoriation (Ex), and lichenification (L) depending on their severity. These 4 body regions are assigned a score of 0–3 according to the severity: 0 representing none, 1 representing mild, 2 representing moderate, and 3 representing severe. The EASI scores range from 0 to 72, and are calculated using the following formula:  $EASI = 0.1 \times (E_H + I_H + Ex_H + L_H) \times A_H + 0.2 \times (E_{UL} + I_{UL} + Ex_{UL} + L_{UL}) \times A_{UL} + 0.3 \times (E_T + I_T + Ex_T + L_T) \times A_T + 0.4 \times (E_{LL} + I_{LL} + Ex_{LL} + L_{LL}) \times A_{LL}$  (19, 20).

### Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) scale was developed by Finlay and Khan in 1994 and is currently the most frequently used instrument for assessing the quality of life in patients with dermatologic conditions (21). Each question of this scale has four options: “not at all”, “a little”, “a lot”, or “very much”, which correspond to scores of 0, 1, 2, and 3, respectively. A response of “not relevant” is scored as “0”. The DLQI score is computed by summing the scores for each question, ranging from a minimum of 0 to a maximum of 30 points.

### Statistical analysis

For this analysis, epidemiological data, clinical data, itch-related data, severity of AD, and the quality of life of the patients were summarised using descriptive statistics. Continuous variables, such as age, were expressed as mean  $\pm$  standard deviation. Categorical variables were assessed based on the number of patients and the percentage within respective categories of the dataset. Spearman's correlation was used to evaluate the association between the analysed average and maximum itch intensities and the EASI and DLQI scores. After analysing the differences in sex, age, educational level, age at first onset, and family history of AD using one-way analysis of variance with EASI and DLQI scores as dependent variables, a multivariate analysis of significant correlations was performed using a generalized linear model. The proportions of patients who experienced itching and the most itchy at different times were compared using Cochran's Q. Significance values have been adjusted by Bonferroni correction for multiple testing. A two-sided  $p < 0.05$  was considered statistically significant. All statistical analyses were performed using SPSS (version 25.0; IBM Corp, Armonk, NY, USA).

## RESULTS

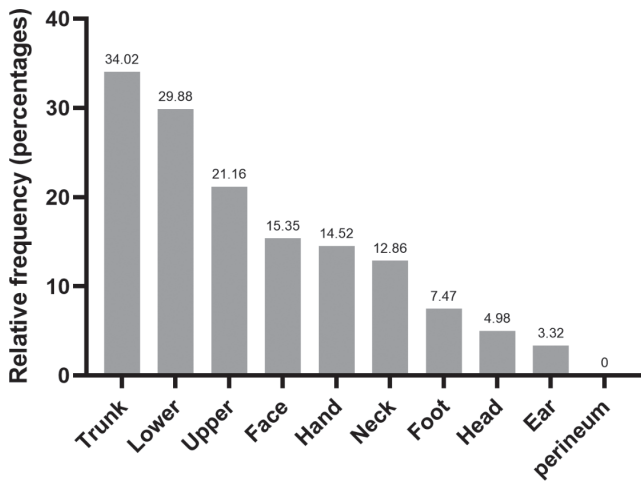
### Participant characteristics

Among the 241 adults included in this study, 134 (55.60%) were females and 107 (44.40%) were males. The mean age was  $44.89 \pm 19.61$  years (median age 40 years [18 to 87]). Education levels included 35 (14.52%) primary school and below, 48 (19.92%) junior high school, 60 (24.90%) high school, and 98 (40.66%) college and above.

**Table 1. Participant characteristics and analysis of differences in Dermatology Life Quality Index (DLQI) and Eczema Area and Severity Index (EASI) scores**

Variables		DLQI <i>p</i>	EASI <i>p</i>
Sex, <i>n</i> (%)		0.638	0.004*
Male	107 (44.40)		
Female	134 (55.60)		
Age, years, mean $\pm$ SD	44.89 $\pm$ 19.61	0.404	0.051
Education level, <i>n</i> (%)		0.561	0.643
Primary and below	35 (14.52)		
Junior high school	48 (19.92)		
High school	60 (24.90)		
College and above	98 (40.66)		
Age at first onset, <i>n</i> (%)		0.347	0.108
0–2	10 (4.15)		
3–12	12 (4.98)		
13–60	180 (74.69)		
>60	39 (16.18)		
Family history, <i>n</i> (%)		0.819	0.007*
Yes	120 (49.79)		
No	121 (50.21)		

SD: standard deviation. \*Statistical significance level at  $p < 0.05$ .



**Fig. 1. Body distribution of pruritus associated with atopic dermatitis (AD):** percentage of patients with AD experiencing itching in different areas of the body.

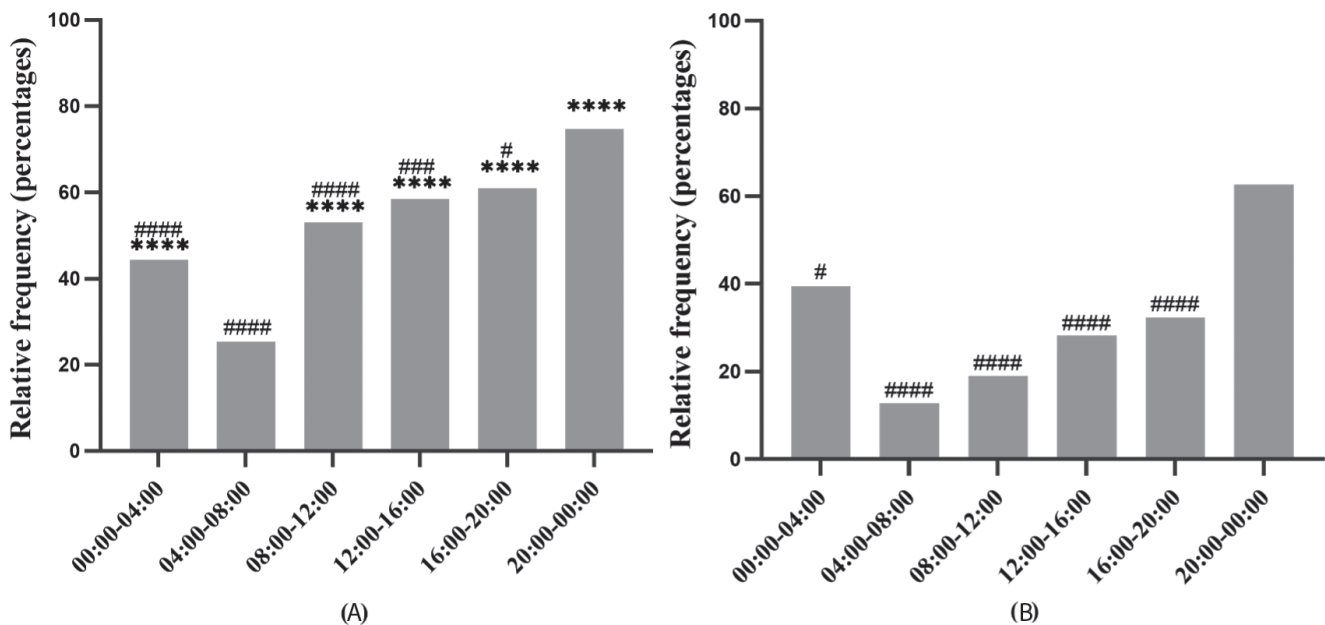
(24.90%) senior high school, and 98 (40.66%) college and postgraduate. A total of 10 (4.15%) patients had a first onset age between 0 and 2 years, and 12 (4.98%) had a first onset age between 3 and 12 years. Furthermore, 180 (74.69%) patients had a first onset between 3 and 60 years of age and 39 (16.18%) had their first onset at ages greater than 60 years. Some 120 (49.79%) patients had a family history of atopy (Table I). We found significant differences in the EASI by sex ( $p=0.004$ ) and family history ( $p=0.007$ ) (Table I). Most patients experienced their first itch mainly on the trunk (34.02%), followed by the lower (29.88%) and upper limbs (21.16%), face (15.35%), hands (14.52%), neck (12.86%), feet (7.47%), head (4.98%), and ears (3.32%); No patients experienced their first itch on the perineum (Fig. 1).

### Circadian rhythm of itch

Patients were found to experience itchiness at any time of the day. Notably, a significant percentage of patients (74.69%) felt itchy between the hours of 20:00 and 00:00, 44.40% between 00:00 and 04:00, 25.31% between 04:00 and 08:00, 53.11% between 08:00 and 12:00, 58.51% between 12:00 and 16:00, and 61.00% between 16:00 and 20:00 (Fig. 2A). The highest percentage of patients (62.66%) experienced the maximum itch intensity between 20:00 and 00:00, 39.42% of patients felt the maximum itch intensity between the hours of 00:00 and 04:00, 12.86% between 04:00–08:00, 19.09% between 08:00–12:00, 28.22% between 12:00–16:00, and 32.37% between 16:00–20:00 (Fig. 2B). The Cochran Q test showed that the proportions of patients who experienced itching and the most itchy at different time periods both differed significantly ( $Q=169.32$ ,  $Q=75.85$ , respectively;  $p<0.05$ ). Further analysis of multiple comparisons showed that the proportion of patients who experienced itchy was significantly higher at 20:00–00:00 than at other time periods ( $p<0.05$ ), and the proportion of patients who experienced itchy was significantly lower at 00:00–04:00 than at other time periods ( $p<0.05$ ) (Fig. 2A). The proportion of patients who experienced the most itchy was significantly higher at 20:00–00:00 than at other time periods ( $p<0.05$ ) (Fig. 2B).

The above trends showed that adult patients with AD may experience itchiness at any time of the day. However, notably, the highest number of patients reporting itching with the maximum itch intensity within the 20:00–00:00 time period.

The average and maximum itch intensity scores were  $5.48 \pm 1.69$  and  $7.09 \pm 1.70$ , respectively. The EASI was



**Fig. 2.** (A) Time period during which the patient experiences itching; (B) time period during which the patient experiences maximum itching. \*\*\*\* $p < 0.0001$  vs 04:00–08:00, # $p < 0.05$ , ### $p < 0.001$ , #### $p < 0.0001$  vs 20:00–00:00.

**Table II. Correlation between Dermatology Life Quality Index (DLQI) scores and average and maximum itch; Eczema Area and Severity Index (EASI) scores and average and maximum itch**

	DLQI <sup>a</sup>		EASI <sup>b</sup>	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Average itch intensity <sup>c</sup>	0.582	<0.001*	0.539	<0.001*
Maximum itch intensity <sup>d</sup>	0.533	<0.001*	0.517	<0.001*

<sup>a</sup>Total scores range from 0 to 30, with higher scores indicating poorer quality of life. The DLQI was  $10.62 \pm 5.38$ . <sup>b</sup>Total scores range from 0 to 72, with higher scores indicating more severe conditions. The EASI was  $9.40 \pm 10.11$ . <sup>c</sup>Total scores ranged from 0 to 10, with higher scores indicating greater itching. The average itch intensity was  $5.48 \pm 1.69$ . <sup>d</sup>Total scores ranged from 0 to 10, with higher scores indicating greater itching. The maximum itch intensity was  $7.09 \pm 1.70$ .

\*Statistical significance level at  $p < 0.05$ .

significantly and positively correlated with the average ( $r=0.539$ ,  $p<0.001$ ) and maximum itch intensities ( $r=0.517$ ,  $p<0.001$ ), whereas the DLQI was significantly and positively correlated with the average ( $r=0.582$ ,  $p<0.001$ ) and maximum itch intensities ( $r=0.533$ ,  $p<0.001$ ) (Table II). Males ( $B=0.285$ , 95% CI: 0.094 to 0.476,  $p=0.003$ ), family history ( $B=0.287$ , 95% CI: 0.096 to 0.478,  $p=0.003$ ) and average itch intensity ( $B=0.204$ , 95% CI: 0.096 to 0.313,  $p<0.001$ ) were associated with EASI scores (Table III). The average itch intensity ( $B=0.179$ , 95% CI: 0.112 to 0.246,  $p<0.001$ ) was associated with DLQI scores (Table IV).

## DISCUSSION

The results of this study showed that itching in patients with AD follows a typical circadian rhythm. Most patients felt the most frequent and the most severe itch during the 20:00–00:00 time period, whereas the least number of patients felt itching during the 04:00–08:00 period. The EASI and DLQI of patients with AD correlated with the average and maximum itch intensities. In addition, this study found that males, family history and average itch intensity were all significantly correlated with EASI scores. It suggests that we need to consider the impact of gender, genetic factors and itch symptoms on disease when assessing and treating AD. At the same time, the average itch intensity was also significantly correlated with the DLQI scores, indicating that itch symptoms not only affect the patient's condition, but may also have a significant impact on their quality of life. Therefore, future research and clinical practice should focus on these factors and explore more effective treatment strategies to comprehensively improve patients' condition and quality of life.

The incidence of scratching is lower during orthodox deep sleep (22, 23). Ebata et al. found in a videotaped

study of nighttime scratching that patients with AD experienced itching leading to scratching more in the first half of the night than in two-thirds of the second half of the night (24). A questionnaire by Yosipovitch et al. showed that 65% of patients with AD had frequent itching during the night, and only 20% reported a high frequency of itching during the morning (12). The results of our study are consistent with those of the above studies, showing that itching increases at night in patients with AD. In previous studies, instrument tests (such as video or bracelet monitors) and questionnaires have been widely used to evaluate itching. Instrument tests can reflect itch more objectively and directly, but the operation is complicated and time-consuming, which is not suitable for large-scale investigation. In contrast, the questionnaire has the advantages of low cost, simple operation, and easy implementation, and is more suitable for large-scale investigation. For specific populations with limited communication abilities, such as paediatric patients with AD, instrumental tests may be a more appropriate choice, while, for adult AD patients who can communicate effectively, questionnaire survey is more efficient and convenient (12, 24). In contrast to previous questionnaire studies, our research focused uniquely on the 24-h itch pattern in adult patients with AD. Previous studies have generally focused on night-time itching and not on specific time periods that extend the analysis throughout the day. By examining the complete circadian cycle, we uncovered a more accurate and comprehensive depiction of itch patterns in AD, which may have significant implications in the management and treatment of the disease. The circadian rhythm of itch that we identified indicates that there are peak times during which patients are more susceptible to itching. These findings may lead to targeted timing of interventions and medication dosing to provide maximum relief when patients are most affected.

**Table III. Generalized linear model of influencing factors on the Eczema Area and Severity Index (EASI) score**

Parameter	B	SE	95% CI	Wald $\chi^2$	<i>p</i>
(Intercept)	0.156	0.224	-0.283,0.595	0.483	0.487
Male	0.285	0.097	0.094,0.476	8.557	0.003*
Female	-	-	-	-	-
Family history (YES)	0.287	0.097	0.096,0.478	8.677	0.003*
Family history (NO)	-	-	-	-	-
Average itch intensity	0.204	0.055	0.096,0.313	13.753	<0.001*
Maximum itch intensity	0.078	0.057	-0.035,0.190	1.837	0.175

SE: standard error; CI: confidence interval. \*Statistical significance level at  $p < 0.05$ .

**Table IV. Generalized linear model of influencing factors on the Dermatology Life Quality Index (DLQI) score**

Parameter	B	SE	95% CI	Wald $\chi^2$	<i>p</i>
(Intercept)	1.332	0.128	1.081, 1.583	108.386	<0.001
Average itch intensity	0.179	0.034	0.112, 0.246	27.751	<0.001*
Maximum itch intensity	<0.001	0.034	-0.065, 0.066	<0.001	0.990

SE: standard error; CI: confidence interval. \*Statistical significance level at  $p < 0.05$ .

Despite recent significant improvements in the understanding of AD and itching, no effective clinical treatments have been found to control itching. The treatment of AD remains challenging and presents an urgent need for new, effective, safe, and targeted therapies. Our findings and further studies may lead to optimized options for clinical pharmacotherapy, such as chronotherapy, which has been validated for its effectiveness and is commonly used in other atopic disorders (e.g., nocturnal asthma) (25, 26). Chronotherapy improves the efficacy and decreases the side effects of existing medications and reduces the financial burden on the patient (13, 14, 27). Notably, our study population was recruited from a single hospital; therefore, the circadian rhythm of itching found in our study may be more pronounced than that reported in studies involving multiple settings. We must consider the issue of recall bias, which arises when participants rely on their memories to report their itching experiences. Memories are often subjective and can be influenced by various factors, such as the passage of time or emotional associations. This can lead to inaccuracies in the reported timing and intensity of itching symptoms. Therefore, in order to reduce the recall bias of time period, we set the time period to a wider 4-hour interval in order to reduce the recall bias of itchy intensity. Subsequent studies are required in which the time period is shortened to elucidate the temporal pattern of itching more precisely.

Consistent with the results of other studies, we found that the EASI and DLQI were associated with itch intensity in patients with AD, with higher intensity of itching associated with higher AD severity and lower quality of life (4, 28, 29). Therefore, controlling itching may reduce the severity of AD and improve quality of life. In our study of adult patients with AD, we found that males had higher EASI scores than females, which may be related to gender-specific behaviours and lifestyles. Our study also revealed that the EASI scores were higher in patients with a family history of atopy than the scores of patients without a family history of atopy. Therefore, when treating patients with a family history of atopic disease, clinicians must consider the family history and characteristics of the patient's current disease process. In addition, the immediate family members of patients with AD should be encouraged to perform basic skin moisturization and avoid skin irritants as preventative measures.

In conclusion, our study demonstrated that itch in patients with AD follows a circadian rhythm. The time period of 20:00–00:00 had the highest frequency of

itching and the most severe itching, whereas the period of 04:00–08:00 had the lowest itch frequency. In addition, our study also demonstrated a correlation between EASI and DLQI scores and itching, and identified male and atopic family history as key factors influencing EASI scores. Our study and further studies may lead to the development of novel, personalized, and targeted temporal therapy strategies for the treatment of itching in patients with AD, reducing the severity of the disease and improving the quality of life of patients.

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*The authors have no conflicts of interest to declare.*

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