Evaluating factor associated with severe and uncontrolled asthma in childhood asthma in the lower northern Thailand

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To identify factors associated with severe and uncontrolled asthma in childhood asthma in Phitsanulok, Thailand

METHODS

A cross-sectional study was undertaken involving 264 children with asthma, ranging in age from 1 to 18 years. These participants were selected from pediatric clinics in three hospitals located in the lower northern Thailand. The primary objective was to assess these children for any allergies associated with asthma and to inquire about asthma-related symptoms using a questionnaire adapted from a validated Thai version of the ISAAC questionnaire. Furthermore, the study involved supplementary inquiries about food allergies, and risk factors, followed by the administration of a skin prick test to evaluate factors potentially associated with severe and uncontrolled asthma.

RESULTS

Among asthmatics, 76.2% experienced the onset of symptoms before the age of 4. Within 12 months, the occurrence of nocturnal wheeze, night cough, severe wheeze and exercise-induced wheeze was 69.8%, 67.6%, 30.1%, and 50% respectively. Emergency room visits and hospitalizations due to asthma exacerbation were 80.5% and 66% of the subjects. From the binary logistic regression, factors found to be associated with the higher rates of severe asthma were history of antibiotic use >1 per year (AOR, 2.074; 95% CI, 1.002 to 4.294) and history of pneumonia (AOR, 2.408; 95% CI, 1.278 to 4.536) while residence surrounded by grass field was found to be associated with the low rate of severe asthma (AOR, 0.341; 95% CI, 0.151 to 0.769). Furthermore, we also found that history of pneumonia was the only factor associated with the higher rate of emergency room visit (AOR, 4.267; 95% CI, 1.892 to 9.623) and hospitalization (AOR, 4.707; 95% CI, 2.417 to 9.168).

CONCLUSION

We found that factors linked to elevated rates of severe asthma, including a history of antibiotic use exceeding one per year and a history of pneumonia. Conversely, residing in an area surrounded by grass fields was associated with a lower rate of severe asthma. Additionally, our findings indicate that a history of pneumonia was the sole factor correlated with increased rates of emergency room visits and hospitalizations.

INTRODUCTION

Asthma is a significant global health concern, especially in childhood, where it ranks as the most prevalent chronic disease. The global prevalence of asthma in children aged 6–7 and 13–14 is 9.1% and 10.2%, respectively.[1] In Thailand, prevalence varies, with rates of 8.3% in Chiang Mai and 13.5% in Bangkok.[2,3] Poorly managed asthma disrupts sleep, daily activities, and school attendance, impacting overall well-being.[4] Severe or uncontrolled asthma also raises the risk of morbidity and mortality.[4]

Numerous factors, including nutrition, allergen exposure, tobacco smoke, and psychosocial influences, contribute to childhood asthma.[4,5] Multifaceted interventions to reduce allergen exposure, have been effective in reducing asthma risk and prevention of asthma.[6–10] Identifying risk factors and allergen sensitization in Thai asthmatic children is essential. A Phitsanulok study on adults found that maternal smoking during pregnancy, family smoking, and family history of allergy were asthma risk factors. Having a nearby rice field reduced the risk.[11] Skin tests in this study showed allergen sensitization in 87.9% of asthmatic adults, with common allergens including house dust mites, cockroaches, and more.[11] In Bangkok, 74% of asthmatic children had positive skin prick tests to allergens, including house dust mites, cockroaches, and others.[12] In Chiang Mai, common allergens among children with allergies included house dust mites and cockroaches.[13]

However, information is lacking on asthmatic children in lower northern Thailand, specifically Phitsanulok and Uttaradit provinces. This study aims to investigate asthma symptoms, allergies, severity, risk factors, and allergen sensitization among asthmatic children in these regions, providing valuable insights for better asthma care and prevention.

METHODS

STUDY DESIGN AND POPULATION

This study was a cross-sectional survey involving 264 asthmatic children aged 1 to 18 years who visited a pediatric outpatient clinic in either one of the 3 hospitals located in lower northern Thailand from 2003 to 2009. The sample size of asthmatic children was calculated from the proportion of severe asthmatic children in the previous ISAAC study conducted in Bangkok,[14] which was 15.4%. with a confidence level of 95% and margin of error within ±5%. All asthmatic children were recruited on the visiting day of the pediatric allergist at the clinic. The participating hospitals included Buddhachinaraj Hospital, Naresuan University Hospital and Uttaradit Hospital. These children were diagnosed with asthma by pediatricians at their local hospitals. This study was reviewed and approved by Naresuan University Institutional Review Board (NU-IRB).

ASTHMA, ASTHMA RELATED SYMPTHOMS AND RISK FACTORS

In our data collection process, we evaluated a range of factors related to asthma and its associated conditions among the children. These assessments covered allergic diseases like allergic rhinitis, allergic rhinoconjunctivitis, atopic dermatitis, and asthma-related symptoms. To gather this information, we employed questions adapted from a validated Thai version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.[3,14–16] Furthermore, we investigated additional aspects of asthma, including the onset of the condition, the presence of exacerbations, and inquiries regarding potential food allergies. The identification of uncontrolled asthma relied on criteria such as emergency room visits or hospitalizations due to asthmatic symptoms. Our exploration of risk factors was comprehensive, covering term delivery, breastfeeding history,

Table 1. Characteristics of the 264 children

Characteristic	Value
Age–month	
Median	96
Interquartile range	50.0–135.5
Male–no. (%)	179 (67.8)
Onset of asthma before 4 years of age	195 (76.2)
Positive response for asthma-related symptoms in the past 12 months–no. (%)	
Wheezing attacks≥12 times	43 (16.7)
Night wheeze	178 (69.8)
Severe asthma	78 (30.1)
Exercise wheeze	130 (50.0)
Night cough	175 (67.6)
Concomitant allergic diseases–no. (%)	
Allergic rhinitis	180 (68.2)
Allergic rhinoconjunctivitis	102 (38.6)
Allergic dermatitis	75 (28.4)
Food allergy	58 (22.4)
Term delivery	215 (84.0)
Breast feeding	217 (85.4)
Smoking during pregnancy	20 (7.6)
Family smoking	117 (44.5)
Family history of allergy	209 (79.2)
Pets	178 (67.7)
History of antibiotics use>1 per year	186 (70.7)
History of pneumonia	126 (51.9)
Residence surrounded by grass field	56 (21.2)
Residence surrounded by rice field	101 (38.3)
Residence surrounded by grass bush	102 (38.6)
Allergen sensitization	221 (83.7)

family history of allergies or smoking, household environment including smoking, antibiotic usage, and history of pneumonia. To assess these factors, we utilized a risk factor questionnaire that had been previously employed in our adult study.[11] The self–reported responses from the participants were all recorded onto a spreadsheet ready for the analysis.

SKIN PRICK TEST

Furthermore, the children were scheduled for a skin prick test using a standard panel of 19 common allergen extracts from Greer Laboratories (NC, USA). These allergens included *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), American cockroach, Bermuda grass, Johnson grass, careless weed, acacia spp., standardized cat hair, dog epithelia, Alternaria tenuis, Cladosporium herbarum, Penicillium mix, Aspergillus mix, shrimp, fish mix, cow's milk, egg white, soybean, and peanut. The negative control consisted of 50% glycerin, while the positive control was 10 mg/ml histamine dihydrochloride. A skin test was considered positive if the wheal size (average of the two longest orthogonal dimensions) was at least 3 mm larger in diameter than the negative control.

TREATMENT OUTCOMES

In the present study, we tried to identify the link between the identified factors and treatment outcomes in terms of severe asthma which was defined as symptoms of wheeze or difficulty breathing that were very severe leading to talking

in 1–2 words continually or inability to complete sentences in one breath, according to ISAAC questionnaire,[3,14–16] and uncontrolled asthma. For uncontrolled asthma was defined as asthma exacerbation requiring an emergency room visit or hospitalization.[4]

STATISTICAL ANALYSIS

We conducted a comprehensive analysis of various parameters, employing both descriptive and inferential statistics. This analysis included the assessment of the frequency of asthma–related symptoms, severe asthma cases, asthma exacerbation incidents, allergic rhinitis occurrences, atopic dermatitis cases, food allergies, and skin test reactivity assessments were summarized using descriptive statistics.

To explore the risk factors associated with severe wheezing, severe asthma, and uncontrolled asthma (defined as instances requiring emergency room visits or hospitalization due to asthma exacerbation), we utilized a binary logistic regression, a form of inferential statistics. This statistical procedure was executed using the STATA software package. The outcomes of this analysis were reported in terms of adjusted odds ratios (AOR) along with their respective 95% confidence intervals (CI), employing both descriptive statistics to summarize the data and inferential statistics to draw meaningful conclusions.

RESULTS

There were 179 males (67.8%) and 85 females (32.2%) in the study. The age range of the participants varied from 1 year and 3 months to 17 years and 6 months. Of all subjects, 32.2% were 5 years of age and younger, 36% were between 5 and 10 years of age, and 31.8% were older than 10 years of age. The majority of asthmatic children (76.2%) had their onset of symptoms before the age of 4, while 68.0%, 51.6%, and 34.0 % experienced the onset of asthma before the ages of 3, 2, and 1 year, respectively.

Table 1 displays the asthma–related symptoms and severity of asthma over the past 12 months. Among asthmatics, 45% experienced at least 4 wheezing attacks within the past year, and 16.7% had wheezing attacks occurring more than once a month. It was observed that a majority of the subjects did not have well-controlled asthma symptoms in the past 12 months, as evidenced by high prevalence of nocturnal wheeze affecting sleep (69.8%) and night cough without respiratory tract infection (67.6%). This study revealed that within 12 months 30.1% of the participants had severe asthma symptoms that impeded their ability to speak, while 50% of the subjects exhibited exercise-induced wheezing. The subjects reported allergic rhinitis and allergic rhinoconjunctivitis at rates of 68.2% and 38.6%, respectively.

Of all asthmatic children, 80.5% reported breathing difficulties requiring emergency room visit with 17.2% having at least 6 visits per year (Table 2). Furthermore, 66% of all subjects had been hospitalized due to asthma exacerbation, with 11.6% experiencing at least 6 hospitalizations per year. In the past 3 years, 74.7% of 75 subjects reported wheezing episodes that necessitated emergency room visits, while 57.3% required hospitalization.

Over a 12–month period, the peak rhinitis symptoms occurred in November, December, and January, affecting 36.4% to 37.1% of subjects, while the least rhinitis symptoms occurred in March, April, May and June, affecting 18.9% to 24.2% of subjects. These findings are consistent with other surveys conducted in the Thai population.[14,16] Among asthmatic subjects with allergic rhinitis, 54.2% experienced nasal symptoms that moderately or severely affected their daily activities, while 38.0% reported mild disturbances in their daily activities. The

Table 2. Uncontrolled asthma

Positive response to	Emergency room visit	Hospitalization
	No. (%)	
Since diagnosis (n=264)	211 (80.5)	173 (66.0)
In the past 3 years (n=75)	56 (74.7)	43 (57.3)

prevalence of concomitant atopic dermatitis was 28.4%, which represents higher prevalence compared to general pediatric population in previous Thai children survey.

In terms of food allergy, 22.4% reported allergic symptoms following food ingestion. The common reactions involved respiratory (44.1%), dermatologic (42.4%), and gastrointestinal systems (30.5%). Respiratory symptoms included sneezing, itchy nose, itchy eyes, runny nose, nasal congestion, cough, chest tightness, and breathing difficulty. The dermatologic symptoms manifested as itchy skin, itchy rash, urticaria, rash around the mouth, angioedema. The gastrointestinal symptoms included itchy throat, abdominal pain, nausea, vomiting, and diarrhea. The most frequently reported food triggers for these reactions were shrimp, shellfish, crab, fish, milk, egg and peanut of 51.2%, 41.5%, 24.4%, 19.5%, 14.6%, 9.8% and 4.9%, respectively.

From the binary logistic regression (Table 3), factors found to be associated with the higher rates of severe asthma were history of antibiotic use >1 per year (AOR, 2.074; 95% CI, 1.002 to 4.294) and history of pneumonia (AOR, 2.408; 95% CI, 1.278 to 4.536) while residence surrounded by grass field was found to be associated with the low rate of severe asthma (AOR, 0.341; 95% CI, 0.151 to 0.769) (Table 3). Furthermore, we also found that history of pneumonia was the only factor associated with the higher rate of emergency room visit (AOR, 4.267; 95% CI, 1.892 to 9.623) and hospitalization (AOR, 4.707; 95% CI, 2.417 to 9.168). Mean while, as asthmatic children grew older, their rate of hospitalization decreased (AOR, 0.987; 95% CI, 0.980 to 0.993).

The skin prick test reaction confirmed that 83.7% of our asthmatic subjects had positive reactivity to at least one allergen. Three most commonly positive allergens were indoor allergens such as Df, Dp, and American cockroach, with reactivity rates of 64.4%, 59.1%, and 54.0% respectively (Figure 1). In descending order, the other allergens that showed positive reactivity were as follows: standardized Bermuda grass (31.4%), Johnson grass (30.7%), *Careless weed* (27.4%), standardized cat hair (27.3%), *Acacia spp* (25.1%), shrimp (24%), dog epithelia (21.3%), *Alternaria tenuis* (19.1%), *Cladosporium herbarum* (10.0%), Aspergillus mix (8.5%), egg white (6.5%), cow's milk (6.5%), fish mix (6.2%), *Penicillium* mix (6.2%), and soybean (3.3%). Interestingly, the subjects demonstrated higher sensitivity to grass pollens compared to animal dander, which differed from another study conducted in Bangkok,[17] but was similar to a study conducted in Chiang Mai.[13]

DISCUSSION

Most of the asthmatic children (83.7%) in our study exhibited allergic asthma, as evidenced by a significantly high allergic skin test reaction. This result emphasized atopy with allergic sensitization as an important predisposing factor in childhood asthma. Nearly 80% of the asthmatic participants experienced the onset of asthmatic symptoms prior to the age of 4, supporting the concept of the

Table 3. Factor associated with severe and uncontrolled asthma

Factor	Severe asthma	Severe asthma	Hospitalization
	Adjusted odds ratio (95% confidence interval)		
Age–yr	0.998 (0.992–1.005)	0.992 (0.984–1.000)	0.987 (0.980–0.993)
Male	1.500 (0.781–2.878)	1.425 (0.667–3.043)	0.673 (0.342–1.327)
History of antibiotics use>1 per year	2.074 (1.002–4.294)	0.470 (0.193–1.141)	0.573 (0.275–1.193)
History of pneumonia	2.408 (1.278–4.536)	4.267 (1.892–9.623)	4.707 (2.417–9.168)
Smoking during pregnancy	1.670 (0.499–5.585)	0.422 (0.098–1.805)	0.310 (0.089–1.074)
History of Family smoking	0.834 (0.446–01.561)	0.949 (0.451–1.995)	1.299 (0.682–2.473)
Term delivery	0.996 (0.438–2.218)	0.795 (0.273–2.314)	1.424 (0.609–3.330)
Breast feeding	1.297 (0.533–3.156)	2.119 (0.746–6.023)	1.051 (0.390–2.834)
Family history of allergy	1.250 (0.5970–2.618)	1.359 (0.574–3.215)	0.710 (0.323–1.560)
Pets	1.213 (0.597–2.618)	1.145 (0.512–2.560)	1.107 (0.556–2.204)
Residence surrounded by grass field	0.341 (0.151–0.769)	1.339 (0.516–3.473)	0.787 (0.374–1.658)
Residence surrounded by rice field	0.731 (0.382–1.401)	0.926 (0.428–2.003)	1.313 (0.672–2.562)
Residence surrounded by grass bush	1.692 (0.892–3.209)	1.044 (0.484–2.254)	0.842 (0.434–1.633)

The adjusted odds ratios displayed in the present table were calculated using binary logistic regression, with the outcomes being categorized as severe asthma, emergency room visits, and hospitalizations. The covariates for each model are listed as factors in the first column.

"allergic march." This phenomenon suggests a natural progression of allergies during infancy and childhood, with asthma typically manifesting before the age of 5.[18] The high occurrence of nighttime wheezing and coughing, along with frequent wheezing episodes over the past year, generally indicates a poor control of asthma symptoms.[4] High rates of severe asthma symptoms, emergency room visits, and hospitalizations for asthma exacerbations were also observed. It is important to note that this study was conducted many years ago, during a period when the usage of inhaled corticosteroids, especially in rural areas, was limited. However, the widespread use of inhaled corticosteroids has increased substantially in recent years, making it interesting to observe the potential improvements in asthma control. Exercise-induced wheeze in our asthmatics was lower compared to other reports.[19] showing a 90% prevalence of exercise-induced asthma in asthmatic individuals, but was higher than in the general pediatric population.[2,14] As anticipated, our asthmatic children had a higher prevalence of concomitant allergic rhinitis and allergic rhinoconjunctivitis compared to non–asthmatic children, which is consistent with previous studies.[3,11] These studies have demonstrated that allergic rhinitis and rhinoconjunctivitis are risk factors for asthma, with a 1.7–1.8 fold increase in frequency among asthmatic subjects.

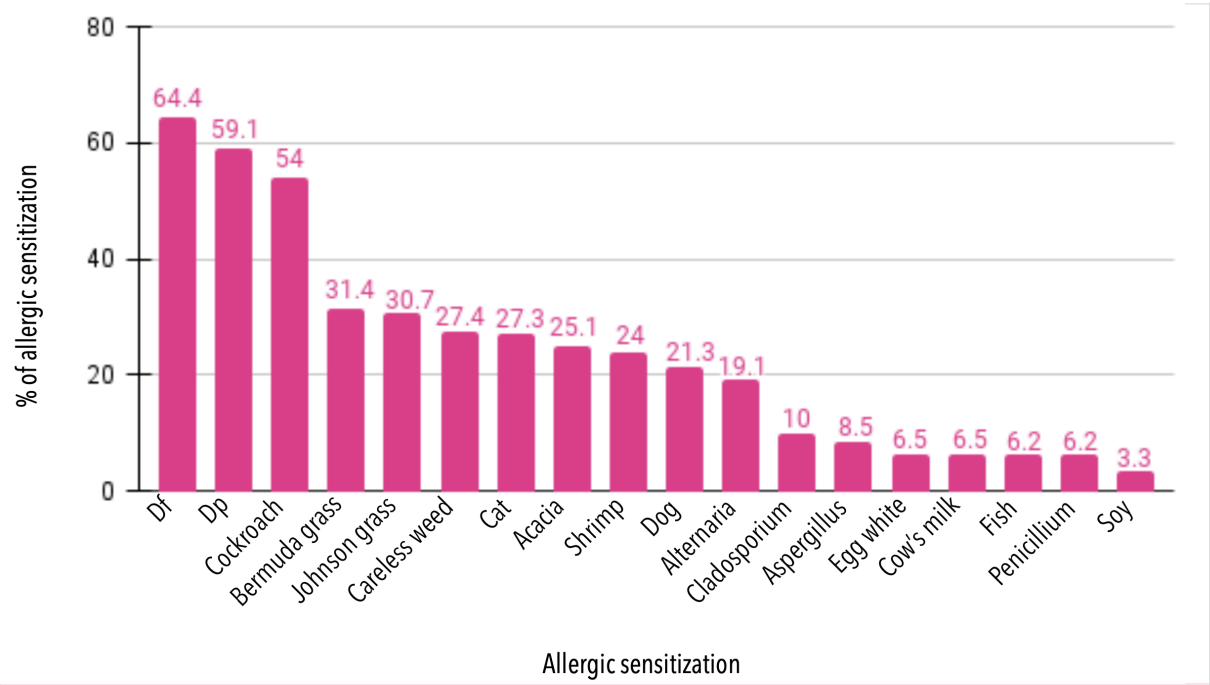

Figure 1. Percentages of allergic sensitization in asthmatic children (n=264)

Our study revealed a higher prevalence of food allergy among our asthmatic children compared to the general population, with respiratory symptoms being the most commonly reported allergic reaction. This finding supports previous observational studies indicating that the frequency of food sensitization in children with asthma is higher than expected in the general population.[20] Symptomatic food sensitization has been associated with asthma in children, particularly when multiple food sensitizations or severe food allergies are present.[21] Moreover, children with food allergies are at a higher risk of asthma–related morbidity, including daytime symptoms, hospitalizations, and a lower percentage of predicted FEV1.[22] Additionally, an increase in food sensitization and food allergy is indicative of persistent asthma and severe asthma attacks.[23] Asthma exacerbations triggered by food ingestion are more common in asthmatic children with food allergies,[20] correlating with our patients whose chest tightness and breathing difficulty were prominent allergic reactions to food.

Our study identified pneumonia as a significant predisposing factor for severe asthma and asthma exacerbation. One study demonstrated that individuals with a history of either typical or atypical pneumonia exhibited increased asthma prevalence.[24] Additionally, another study revealed that early pneumonia is associated with impaired airway function and an increased risk of developing asthma.[25] Our study found that antibiotic use emerged as a significant risk factor for severe asthma, corroborating previous studies. This association is supported by a cohort study and a meta-analysis, indicating that early-life antibiotic use is linked to an increased risk of asthma.[26,27] However, another systematic review suggested that the correlation between antibiotic use and subsequent development of wheezing/asthma may be weak and overestimated, possibly due to reverse causation and confounding by indication.[28] Living areas surrounded by grass fields showed a significant protective effect against severe asthma in our study. This finding is consistent with our previous study conducted on adults in Phitsanulok,

which demonstrated that residing in areas surrounded by rice fields was associated with a lower risk of asthma development.[11] These findings reinforce the microbiota hypothesis, suggesting that living on a farm or in close proximity to livestock, resulting in a higher microbial load, may provide protection against allergic diseases.[5] Another possible explanation is that reduced exposure to pollutants in grass field environments leads to fewer asthmatic symptoms. Pollutants such as nitric oxide, carbon monoxide, carbon dioxide, formaldehyde, and particulate matter, originating from industries, vehicles, and combustion processes, are typically less prevalent in grass field environments. Previous studies have demonstrated that pollutants, particularly those present outdoors and in areas close to major roads, can have an adverse impact on respiratory health and increase the risk of asthma.[4,29,30] It has also been reported that up to four million new cases of pediatric asthma may be attributed to exposure to traffic-related air pollution.[31]

Regarding allergic sensitization, a significant majority of our asthmatic children exhibited positive skin reactivity (83.7%) to at least one allergen, indicating a high prevalence of allergies among our study participants. Consistent with prior studies conducted in the Thai population focusing on allergic rhinitis and asthma, house dust mites (Df, Dp) remained the most prevalent sensitized allergens, followed by cockroaches.[11-13,17] Interestingly, our study revealed that Bermuda and Johnson grasses were the primary allergenic pollens, surpassing cat and dog dander in terms of sensitization. This result diverges from the allergic rhinitis population in Bangkok, where cat sensitization was more prevalent than pollen sensitization, but aligns with a study conducted in Chiang Mai.[11,13,17] Notably, the percentages of positive skin test reactivity to both grass pollens and cats in our asthmatics were higher compared to the findings from Chiang Mai.[13] and Bangkok studies.[12] These disparities could stem from genetic heterogeneity and increased exposure to grass pollens and cats, as Phitsanulok and Uttaradit are in lower northern Thailand and feature more culturally diverse areas than Bangkok.

The major strength of our study is the first study in asthmatic children in lower northern Thailand on concomitant food allergy, risk factor for severe asthma by questionnaire, and on allergic sensitization by skin prick test. The knowledge can provide physicians to improve care in asthmatic children, prevent asthma development and prevent asthma exacerbation. One limitation of this study is that it was conducted many years ago when there was probably less inhaled corticosteroid use for asthma control. The positive response rates in uncontrolled asthma in our study might be slightly overestimated. Nevertheless, the findings of concomitant allergic diseases, predisposing factors, allergic sensitization in our children likely are not altered over the period of time.

In conclusion most asthmatic children in lower northern Thailand experienced the onset of asthma before the age of 4, and 84% had allergic sensitization. The symptoms substantially were not well controlled. Our study identified antibiotic use and pneumonia as risk factors for severe asthma, while residing in areas surrounded by grass fields appeared to be a protective factor. Furthermore, the prevalence of concomitant allergic diseases, including food allergies, was notably higher among asthmatics. Shrimp emerged as the most allergenic food, and respiratory symptoms such as cough, chest tightness, and breathing difficulties were the most frequently observed allergic reactions to food among asthmatic individuals. House dust mites and cockroaches were the two most prevalent allergens causing sensitization in this population.

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