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Significant factors associated with severity and outcome of an initial episode of acute urticaria in children

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The aim of this study was to determine the predictive factors of severity and duration of an initial episode of acute urticaria in children. This was a retrospective study of 1120 children of < 18 yr who presented to the emergency department (ED) with an initial episode of acute urticaria during the period January 1, 2001, to December 31, 2007. These patients were followed in the ED or outpatient department (OPD) until their symptoms subsided. Variables comprising mild, moderate, and severe urticaria were compared to determine the predictors of severity. The relationships between duration of urticaria and clinical features, including physician-diagnosed causes and treatment modalities, were also analyzed. Significant predictive factors of severity of an initial episode of acute urticaria in children included age, physician-diagnosed causes of urticaria, clinical presentation, coexistent pyrexia or angioedema, and personal allergic history (all $p < 0.001$). The duration of urticaria was dependent on the physician-diagnosed causes and treatment. Inhalants and unknown causes were predictive of longer duration, while contact materials were associated with shorter duration of urticaria ($p < 0.001$). Combination treatment comprising an oral plus injectable form of antihistamine or corticosteroid significantly shortened the duration of urticaria compared to single treatment ($p < 0.001$), especially in children receiving short-term aggressive treatment in the pediatric observation unit (POU) of the ED.

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Key words: acute urticaria; an initial episode; children; etiology; severity; duration

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Acute urticaria is a common disease in the pediatric emergency department (ED). Many parents seek emergency medical treatment for their children when they experience an initial episode of acute urticaria, especially when these children develop severe clinical presentations, including recurrent itching, generalized wheals, swelling of the lips or eyelids, or shortness of breath. Risk factors associated with the severity of urticaria have been investigated in adults but have not been adequately addressed in children (1–3) especially in children with an initial episode of acute urticaria. Although the results of specific laboratory examinations have been shown to be predictors of the severity and duration of chronic urticaria(1, 4), rapid useful methods that can be simply applied in a clinic to predict the severity and duration of an initial episode of acute urticaria in children have not been studied.

The diagnosis of acute urticaria is usually based on detailed history taking and clinical manifestations, such as the presence of transient, well-circumscribed wheals that involve the upper and mid-dermis. Urticarial lesions can be evanescent, disappearing within minutes to hours. Acute urticaria is defined as urticaria that has been present for less than 6 wk (5). A detailed understanding of the factors that may predict the

severity and duration of urticaria will help primary physicians perform appropriate clinical assessments and help parents take care of their children at home. Therefore, the aim of this retrospective study was to determine the factors that could be used to predict the severity and duration of an initial episode of urticaria in children.

Materials and methods

Patient population

During the period January 1, 2001, to December 31, 2007, acute urticaria was diagnosed in 9733 children aged less than 18 yr at the Changhua Christian Hospital, a 2000-bed medical center in central Taiwan. Among those patients, 2088 children underwent medical treatment in the pediatric ED, and 1447 of those children were identified as having had an initial episode of acute urticaria. An initial episode of acute urticaria was defined as urticarial symptoms presenting for less than 6 wk in patients without a history of urticaria. Of the 1447 children who presented with an initial episode of acute urticaria, 327 were excluded from the study because they had been lost to follow up. Therefore, the final study population comprised 1120 patients.

Methods

Patient characteristics were obtained from hospital chart records and included the date of disease onset, age at onset, gender, physician-diagnosed causes, clinical presentations, coexistence with pyrexia, coexistence with angioedema, personal allergic history, treatments, and total duration of urticaria. Children were divided into four age groups: infant (1 month–1 yr), preschool age (2–6 yr), school age (7–12 yr), and adolescent (13–18 yr). The physician-diagnosed causes were divided into seven major categories: (i) medications, (ii) foods, (iii) various infections, (iv) inhalants, (v) insect bites, (vi) contact materials, and (vii) unknown causes. The relationships between these physician-diagnosed causes and an initial episode of acute urticaria were determined by peer review of the patients' medical history and clinical assessments. The physician-diagnosed causes of acute urticaria were determined based on statements made by the patients or their family members about special life events or environmental exposure. For example, either viral or bacterial infection was suspected to be the physician-diagnosed cause when patients presented with urticaria after a recent bacterial or viral infection. Food or medications were suspected to be the physician-diagnosed cause when patients or family members stated that they suffered from skin rash after eating a particular food or taking a particular medication. Unknown causes were suspected when clinical assessments revealed non-specific findings and patients or family members denied any special life event or exposure to environmental stressors such as changes in diet, recent medication use, or contact with animals, plants or special materials.

The clinical presentations of children with an initial episode of acute urticaria included six groups of constitutional symptoms: (i) skin lesions only, (ii) respiratory tract symptoms (cough, rhinorrhea, sore throat, shortness of breath), (iii) urinary tract symptoms (frequency, dysuria, pyuria), (iv) neurologic symptoms (dizziness, vertigo, convulsion, headache, consciousness change), (v) gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation, abdominal pain), and (vi) others. Personal allergic history, including asthma, allergic rhinitis, or atopic dermatitis, was obtained from hospital chart records and statements from patients or family members. The types of medical treatment that improved symptoms were recorded. Antihistamines, either H1-antagonists or H2-antagonists, and corticosteroids were used to treat urticaria in all patients. Epinephrine was used only in children who presented with angioedema or respiratory distress (3, 5–9). Dosages of medications were based on body weight in all cases. Medications were administered via injection only in children who required hospitalization or further observation in the pediatric observation unit (POU). The POU is designed for children who do not require inpatient admission but need to stay in the hospital for further observation and short-term treatment. The patients come directly to the POU from the pediatric ED or outpatient department (OPD) with a set of admission orders and admission notes. Once in the POU, these patients are evaluated, and orders are reviewed by physicians. Patients are discharged from the POU if they are clinically stable. Patients who are not clinically stable during observation are admitted as inpatients.

The total duration of urticaria was defined as the period from the onset of symptoms to the resolution of symptoms. The information on the duration of urticaria was obtained from descriptions recorded by physicians during follow-up in the ED or OPD and from statements provided by patients or family members. The factors associ-

ated with the total duration of urticaria were analyzed.

Acute urticaria was categorized as severe, moderate, or mild based on the number of wheals and the degree of pruritus in the 1120 children who presented with an initial episode of acute urticaria (2). Severe urticaria requiring hospital admission was defined as the presence of extensive wheals (over 50 wheals within 24 h or large confluent areas of wheals) or intensive pruritus. Moderate urticaria requiring observation in the POU was defined as the presence of a moderate number of wheals (21–50 wheals within 24 h) or moderate pruritus. Mild urticaria was defined as the presence of very few wheals or mild pruritus. Once a diagnosis of acute urticaria had been made, ED nurses helped physicians to determine the severity by counting the number of wheals and taking pictures for medical records. In this study, all patients with mild urticaria were discharged home from the ED and did not require hospital admission or observation in the POU. Variables that may be related to mild, moderate, and severe urticaria were analyzed to determine the predictors of the severity of an initial episode of acute urticaria.

Statistical analysis

Data were analyzed by one-way ANOVA and chi-square test. The results of descriptive analyses of independent variables (age, gender, physician-diagnosed causes, clinical presentations, personal allergic histories, and treatments) are reported as percentages and mean ± s.d. Factors that might be associated with the severity of an initial episode of acute urticaria were analyzed by the chi-square test. The relationships between physician-diagnosed causes, treatments, and the duration of urticaria were analyzed by one-way ANOVA. A p-value of less than 0.05 was regarded as significant.

Results

Patient characteristics, physician-diagnosed causes, clinical presentations, and treatments

The 1120 children included in this study comprised 637 boys and 483 girls. They ranged in age from 1 month to 18 yr (mean age, 5.4 ± 4.2 yr). The majority of the children were in the preschool age group (55%), followed by the school age (23.7%), infant (14%), and adolescent (7.3%) groups. Seven major etiologic categories were determined. The most common physician-diagnosed cause was infection (47.9%), followed by foods (23.7%), unknown causes (13%), medications (12.4%), inhalants (1.7%), insect bites (1.2%), and contact materials (0.2%). Among the 1120 children, 384 had personal allergic histories. Allergic rhinitis (21.9%) was the predominant personal allergic history, followed by asthma (8.6%) and atopic dermatitis (3.8%) (Table 1). The triggering agents responsible for the initial episode of acute urticaria caused by infections, medications, and inhalants are reported in Table 2.

Clinical presentations included skin lesions only (45.1%), respiratory tract symptoms

Table 1 Demographics, clinical presentations, and treatments of an initial episode acute urticaria in children

	An initial episode acute urticaria in children (N = 1120)	
	No.	%
Gender		
Male	637	56.9
Female	483	43.1
Age (mean ± s.d., y/o)	5.4 ± 4.2	
Infant	156	14
Pre-school age	617	55
School age	265	23.7
Adolescent	82	7.3
Clinical presentations		
Only skin lesions	505	45.1
Respiratory tract symptoms	464	41.4
Urinary tract symptoms	8	0.7
Neurologic symptoms	4	0.4
Gastrointestinal symptoms	118	10.5
Others	21	1.9
Physician-diagnosed cause of urticaria		
Medications	139	12.4
Foods	266	23.7
Various infections	536	47.9
Inhalants	19	1.7
Insects bite	13	1.2
Contact materials	2	0.2
Unknown causes	145	13
Coexist with pyrexia	328	29.3
Coexist with angioedema	99	8.8
Personal allergic history		
Asthma history	96	8.6
Allergic rhinitis history	245	21.9
Atopic dermatitis history	43	3.8
Treatments		
Antihistamines (oral form/†injection form/both)	792/17/282	72.6/1.6/25.8
Corticosteroids (oral from/†injection form/both)	222/286/65	38.7/49.9/11.4
Epinephrine(SubQ)	14	1.3
Total duration of symptoms	6.6 ± 4.4	
≦ 3 days	157	14
4–7 days	614	54.8
8–14 days	289	25.8
≧ 15 days	60	5.4

†Injection form included intravenous form or intramuscular form.
SubQ, Subcutaneous.

(41.4%), gastrointestinal symptoms (10.5%), urinary tract symptoms (0.7%), and neurologic symptoms (0.4%). Pyrexia was observed in 328 children (29.3%). Urticaria coexisted with angioedema in 99 children (8.8%). The most commonly used medical treatments in the ED were oral antihistamines (71.6% of all children), followed by intravenous (IV) corticosteroids (25.9%), oral plus IV antihistamines (25.5%), and oral corticosteroids (20.1%); only 1.3% of children received subcutaneous epinephrine injections. All antihistamines were H1-antagonists. The mean duration of urticaria was 6.6 ± 4.4 days, but for most children (54.8%), the total duration of urticaria ranged from 4 to 7 days. Only 60 (5.4%) children had symptoms lasting for more than 15 days (Table 1).

Factors associated with the severity of an initial episode of acute urticaria

Of the 1120 children enrolled in this study, mild urticaria was diagnosed in 607 (54.2%) children, moderate urticaria was diagnosed in 202 (18%) children, and severe urticaria was diagnosed in 311 (27.8%) children. Age was significantly associated with the severity of acute urticaria. The percentage of children with moderate or severe urticaria was higher in the adolescent and pre-school age groups than in the infant and school age groups ($p < 0.001$) (Table 3). Medications and various infections were the most common physician-diagnosed causes of moderate and severe urticaria ($p < 0.001$). Children who presented with gastrointestinal symptoms had more severe urticaria ($p < 0.001$). Moreover, coexistence of pyrexia ($p < 0.001$) or angioedema ($p < 0.001$) was a significant predictor of severe urticaria. Finally, acute urticaria was more severe in children without previous allergic history ($p < 0.001$).

Factors associated with the duration of an initial episode of acute urticaria

The mean duration of urticaria was 7.5 ± 5.3 days in patients who were discharged from the ED directly (mild urticaria), 4.8 ± 2.4 days in children who required observation in the POU (moderate urticaria), and 7.1 ± 2.7 days in children who were admitted to the hospital (severe urticaria). There was a significant difference in mean duration between the three groups ($p < 0.001$) (Fig. 1).

The medications administered to the children during the study period included antihistamine, corticosteroid, and epinephrine. Of the patients who received antihistamine (n = 1091), 72.6% received the oral form, 1.6% received the IV form, and 25.8% received oral plus IV forms. Of the patients who received corticosteroid (n = 573), 38.7% received the oral form, 49.9% received the IV form, and 11.3% received oral plus IV forms. Of the patients who received epinephrine (n = 14), all received the subcutaneous form. The method by which the medications were administered influenced the duration of symptoms in children with urticaria. Children who did not receive antihistamine had the longest duration of urticaria (7.7 ± 7.1 days) and children who received oral plus IV antihistamines had the shortest duration (5.2 ± 4.1 days) ($p < 0.001$) (Fig. 2a). In addition, children who received the IV form of corticosteroid treatment had a shorter duration of urticaria than those who received oral corticosteroid (6.4 ± 2.7 days

Table 2. Physician-diagnosed triggering agents caused initial episode of acute urticaria in infections, medications, and inhalants.

Medications (N = 139)	No. (%)	Various infections (N = 536)	No. (%)	Inhalants (N = 19)	No. (%)
NSAID	45 (32.4)	Upper respiratory tract infections	351 (65.5)	Animal feather	9 (47.4)
Ibuprofen	16 (11.5)	*Nasopharyngitis*	229 (42.7)	*Dog*	6 (31.6)
Diclofenac Sodium	11 (7.9)	*Laryngitis*	42 (7.8)	*Chicken*	2 (10.5)
Ketorolac Tromethamine	11 (7.9)	*Rhinosinusitis*	40 (7.5)	*Duck*	1 (5.3)
Acetylsalicylic acid	4 (2.9)	*Tonsillitis*	16 (3)	*Pollen*	7 (36.8)
Others	3 (2.2)	*Others*	24 (4.5)	*Others*	3 (15.8)
Antibiotics	35 (25.2)	Acute gastroenteritis	70 (13.1)		
Vaccine	11 (7.9)	Lower respiratory tract infections	59 (11)		
Acetaminophen	5 (3.6)	Urinary tract infections	19 (3.5)		
Herbs	12 (8.6)	Cellulitis	18 (3.4)		
Antiepileptics	5 (3.6)	Skin infections	12 (2.2)		
Antidiarrheas	7 (5)	Acute otitis media	7 (1.3)		
Antiemetics	3 (2.2)				
Sulfa drug	3 (2.2)				
Others	13 (9.3)				

Table 3. Related factors associated with the severity of an initial episode acute urticaria in children

	An initial episode acute urticaria of children (N = 1120)						
	Mild urticaria (ED discharge) N = 607		Moderate urticaria (POU observation) N = 202		Severe urticaria (Hospital admission) N = 311		
	No.	%	No.	%	No.	%	p-value
Age							
Infant	95	15.7	23	11.7	38	12	<0.001
Pre-school age†	325	53.7	97	47.5	195	62.2	
School age	141	23.5	53	25.7	71	23	
Adolescent†	46	7.1	29	15.1	7	2.7	
Physician-diagnosed cause of urticaria							
Medications†	46	7.6	39	19.3	54	17.4	<0.001
Foods	151	24.8	51	25.2	64	20.6	
Various infections†	281	46.4	95	47	160	51.4	
Inhalants	15	2.5	3	1.5	1	0.3	
Insects bite	6	1	5	2.5	2	0.6	
Contact materials	0	0	2	1	0	0	
Unknown causes	108	17.8	7	3.5	30	9.6	
Clinical presentations							
Only skin lesions	318	52.4	87	43.1	100	32.1	<0.001
Respiratory tract symptoms	251	41.4	88	43.6	125	40.2	
Urinary tract symptoms	7	1.2	1	0.5	0	0	
Neurologic symptoms	0	0	3	1.5	1	0.3	
Gastrointestinal symptoms†	25	4.1	23	11.4	70	22.5	
Others	6	1	0	0	15	4.8	
Coexist with pyrexia†	91	15	68	33.7	169	54.3	<0.001
Coexist without pyrexia	516	85	134	66.3	142	45.7	
Coexist with angioedema†	30	4.9	48	23.8	21	6.8	<0.001
Coexist without angioedema	577	95.1	154	76.2	290	93.2	
With personal allergic history	281	46.3	76	37.6	87	28	<0.001
Without personal allergic history†	326	53.7	126	62.4	224	72	

†Favorable predictors of severe an initial episode acute urticaria in children.
ED, Emergency department; POU, Pediatric observation unit.

vs. 8.4 ± 5.6 days). Furthermore, the oral form plus IV form corticosteroid treatment was associated with the shortest duration of symptoms (5.0 ± 2.6 days) ($p < 0.001$) (Fig. 2b). Epinephrine was administered to only 14 (1.3%) children. Patients who received epinephrine treatment had a significantly shorter duration of urticaria than those who did not receive epinephrine treatment (epinephrine, 4.4 ± 1.2 days vs. no epinephrine, 6.9 ± 4.4 days) ($p < 0.001$) (Fig. 2c).

Physician-diagnosed causes of an initial episode of acute urticaria in children were not only associated with the severity of disease but they also correlated with the total duration of urticaria. The duration of urticaria differed significantly among different physician-diagnosed causes ($p < 0.001$). Inhalants and unknown causes were associated with the longest durations of urticaria (8.6 ± 4.1 days and 8.2 ± 6.1 days, respectively), while contact materials and medications were associated with the shortest durations (3.5 ± 0.7 and 5.8 ± 3.8 days, respectively) ($p < 0.001$) (Fig. 3).

Discussion

Urticaria is a common disease in the pediatric ED and is estimated to affect 15% to 25% of people at some point in their life (5). Many parents ask for emergency medical treatment when their children experience first time attacks of acute urticaria, especially when their children develop severe clinical symptoms, such as intensive pruritus, recurrent generalized wheals, edema of the lips or eyelids, and shortness of breath (10–13). In this study, we determined the predictors of severity and total duration of an initial episode of acute urticaria in children.

We found that various infections and medications were associated with a more severe clinical course of urticaria than other physician-diagnosed causes. Most children with urticaria caused by these two physician-diagnosed causes required hospital admission or observation in the POU. We also found that unknown causes were significantly associated with mild urticaria and

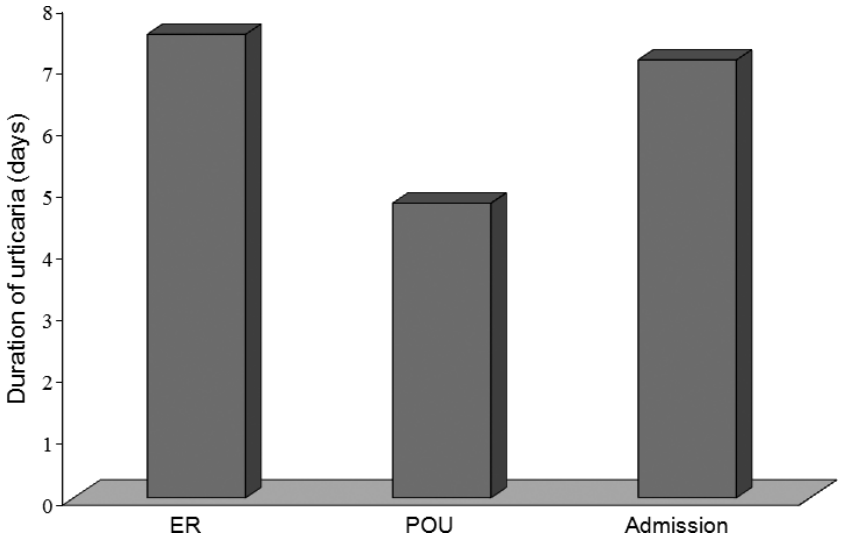

Fig. 1. The mean duration of urticaria differed between patients who were discharged home from the emergency department (ED), patients who were observed in the pediatric observation unit (POU) and those who were admitted to hospital ($p < 0.001$).

that patients with mild urticaria might not require long-term hospital stay.

In addition, we found that age was a significant predictor of severity of urticaria in children. Previous studies have reported that physician-diagnosed causes of acute urticaria in children may differ between age groups (14, 15). However, the relationship between the severity of acute urticaria and the age of children has not been previously evaluated. In this study, we divided patients into four age groups and found that preschool age children and adolescents who suffered an initial episode of acute urticaria had more severe clinical courses than children in other age groups.

The clinical presentations of an initial episode of acute urticaria varied, and most were not associated with the severity of acute urticaria. Skin lesions and respiratory tract symptoms (cough, rhinorrhea, sore throat, shortness of breath) were the most common presenting symptoms of acute urticaria in our study, but these were not directly associated with the severity of the disease. Plumb et al. studied 52 children with urticaria and reported that gastrointestinal symptoms may be associated with urticaria (16). They did not further investigate the relationship between gastrointestinal symptoms and the severity of the disease. In our study, we found that children who presented with gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation, abdominal pain) required POU observation and hospital admission more frequently than patients who presented with other symptoms ($p < 0.001$). Therefore, a severe clinical course should be anticipated in children who present with acute urticaria and gastrointestinal symptoms.

We found that the coexistence of urticaria and pyrexia was associated with more severe form of urticaria. The percentage of children who were admitted to hospital was higher among the group of patients who presented with pyrexia than among those who presented without pyrexia ($p < 0.001$). In addition, all children who presented with urticaria and angioedema had moderate urticaria, and most of them required POU observation (48.5%). Only 21.2% of those children required hospital admission. Short-term observation and treatment for urticaria in the POU is, therefore, recommended for children who present with an initial episode of acute urticaria concomitant with angioedema. In addition, hospital admission should be considered for children who presented with pyrexia and urticaria.

Primary care physicians need to differentiate between urticaria and urticaria as a symptom of anaphylaxis, because the outcomes of these two types of allergic reactions are markedly different (17). In this study, all patients were identified as having had an initial episode of acute urticaria and in some of the patients, urticaria was highly suspected as a symptom of anaphylaxis. We noted that 8.8% ($n = 99$) of the children presented with angioedema and 1.3% ($n = 14$) received epinephrine treatment for respiratory distress.

Studies have shown that personal or first-degree family history of atopy is common among

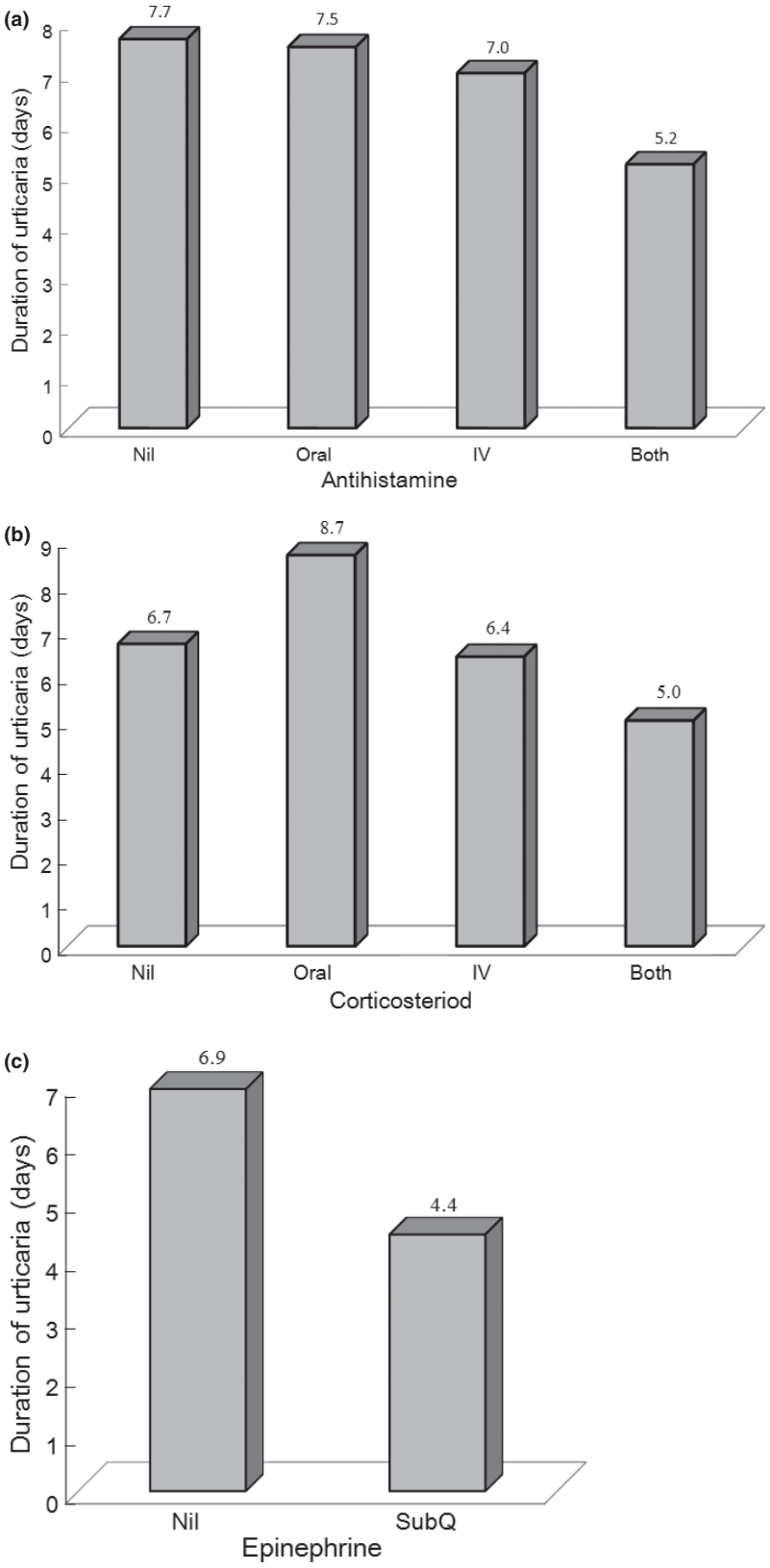

Fig. 2. Duration of urticaria according to different treatments. (a) Antihistamine ($p < 0.001$) (b) Corticosteroid ($p < 0.001$) (c) Epinephrine ($p < 0.001$).

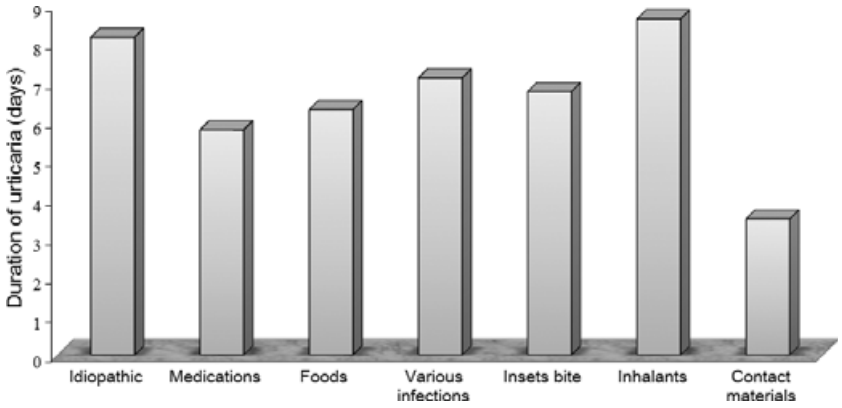

Fig. 3. The duration of urticaria differed significantly between different physician-diagnosed causes of an initial episode acute urticaria in children ($p < 0.001$).

patients with acute urticaria (5). In our study, however, the majority of children (n = 676; 60.3%) did not have a personal allergic history. Furthermore, we found that the frequency of observation in the POU or hospital admission was higher among patients without an allergic history than among those with an allergic history ($p < 0.001$).

We found that the severity of urticaria was associated with the duration of the disease. Children who were discharged home from the ED had the longest duration of urticaria, whereas children who only required observation in the POU had the shortest duration of urticaria ($p < 0.001$). In addition, we found that the duration of urticaria was also associated with different treatment modalities. Most children in the POU received aggressive treatments, including both oral and IV forms of antihistamine or corticosteroid, but patients who were discharged home from the ED only received oral forms of medication. In addition, treatment with IV form antihistamine or corticosteroid was associated with shorter duration of urticaria than treatment with the oral from antihistamine ($p < 0.001$). Furthermore, combined treatment with oral plus IV form antihistamine or corticosteroid was associated with the shortest duration of an initial episode of acute urticaria in children ($p < 0.001$). Overall, aggressive medical treatments and observation in the POU may be useful for controlling an initial episode of acute urticaria in children.

The clinical presentations of an initial episode of acute urticaria vary depending on the physician-diagnosed causes. Knowledge of the various physician-diagnosed causes of urticaria will help primary physicians perform appropriate clinical assessments and predict the duration of urticaria. In this study, we found that contact materials, mediations, and foods were associated with a short duration and that inhalants and unknown factors were associated with a long duration of urticaria. Furthermore, medications and various infections were associated with severe urticaria but not associated with longer duration of urticaria. Inhalants and unknown causes were associated with longer duration of urticaria but not associated with severe urticaria. Overall, the duration and the severity of urticaria varied depending on the physician-diagnosed causes. Therefore, it is important to investigate the physician-diagnosed causes of the urticarial lesions in patients who present with acute urticaria. We suggest that children with acute urticaria caused by medications or various infections should not be discharged prematurely from the ED. Children who present with acute urticaria caused by inhalants or unknown causes should receive aggressive treatments with short-term hospitalization to decrease the total duration of urticaria. Children with moderate to severe acute urticaria should be managed with short-term observation and should receive aggressive treatment in the POU.

Limitations

There were some limitations to this study. First, admitting patients to the hospital for severe itching or because of the presence of multiple skin lesions may not be practical throughout the rest of the world. Hospital resources are simply too precious to allow for such a practice. Therefore, we suggest that moderate to severe acute urticaria be managed with short-term observation and treated aggressively in the POU to avoid recurrent hospital shopping and to decrease the duration of urticaria. The retrospective nature of this study was another limita-

tion. Although the hospital admission criteria for acute urticaria had been clearly defined, the criteria may have been influenced by the duration of symptoms or simply by the admitting practice of the treating physician. Therefore, after peer review of the hospital chart records, 18 children who were admitted to hospital and 10 children who were observed in the POU were excluded from the study, because the severity of urticaria in those patients was difficult to confirm. Similarly, 32 children who presented to the ED with moderate or severe urticaria were excluded from the study, because their parents had refused POU observation or hospital admission for their children.

Conclusion

In this study, we determined several significant factors that may predict the severity of an initial episode of acute urticaria in children. We also found that the duration of urticaria varies depending on the physician-diagnosed causes and that the duration may be shortened if patients receive short-term aggressive treatment with observation in the POU.

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