

ORIGINAL ARTICLE

Factors associated with relapses among patients treated for acute urticaria

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ABSTRACT

The benefit of corticosteroids in acute urticaria is controversial. Our objective was to determine the factors associated with relapses in patients presenting with acute urticaria. A retrospective observational study, including all patients with acute urticaria who visited the angioedema reference center of Academic Public Hospitals – Saint-Antoine in Paris between January 2015 and June 2017, was conducted. The study inclusion criterion was a diagnosis of acute urticaria in an adult patient. The urticaria was spontaneous or inducible urticaria. The primary outcome was relapse at day 7 and the secondary outcome was relapse at week 6. A total of 184 patients with a first episode of acute urticaria were included. Most of the patients were female (66%) with a mean age of 42 ± 16 years. Corticosteroid administration for treatment of acute urticaria was used in 102 (55%) patients. Overall, 85 (46%) patients had relapses after less than 7 days whereas 168 (91%) patients had relapses after more than 6 weeks. In univariate analysis, the rate of corticosteroid administration was significantly higher in cases of relapse after less than 7 days. No difference in relapse rates after more than 6 weeks appeared. In the multivariate analysis, the independent factor associated with relapses after less than 7 days was the administration of corticosteroids as treatment of acute urticaria (odds ratio, 1.93; 95% confidence interval, 1.06–3.57; $P = 0.03$). The prevalence of corticosteroid administration for patients with acute urticaria was high. Corticosteroid administration was an independent risk factor associated with relapses after less than 7 days.

Key words: angioedema, acute urticaria, antihistamines, corticosteroids, emergency department.

INTRODUCTION

Urticaria is defined as a disease characterized by the development of wheals (hives), angioedema or both.¹ According to current classification, urticaria can be classified based on its duration as acute (≤ 6 weeks) or chronic (> 6 weeks) and as spontaneous (no specific eliciting factor involved) or inducible (specific eliciting factor involved).¹ Moreover, acute urticaria can be allergic or not.¹

Although a short course of systemic glucocorticosteroids, which may be helpful to reduce disease duration and/or activity, is included in the treatment guidelines of patients with an acute urticaria, the benefit of corticosteroids was controversial in different studies.¹ On one side, in a low-powered ($n = 43$)

prospective randomized controlled trial with only 5 days follow up, the addition of prednisone to hydroxyzine for 4 days reduced the duration of rash and pruritus.² In a non-randomized cohort study of 109 patients with acute urticaria, symptoms resolved earlier with prednisone than with loratadine.³ On the other side, in a recent double-blind randomized controlled trial, the addition of prednisone to levocetirizine did not improve the symptomatic and clinical response of acute urticaria.⁴ Moreover, only the last trial investigated short-term relapses, without a significantly different rate between the two groups, while corticosteroid treatment was not associated with a decreased relapse rate on additional care within 7 days in a recent retrospective study with allergic reactions.⁵ No long-term follow up was investigated in the three studies,^{2–4} while

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oral steroids might have conferred resistance to antihistamine in chronic urticaria in a prospective study in 17 patients.⁶

The aim of the present study was to determine the factors associated with relapses in patients presenting with acute urticaria.

METHODS

Study design

This retrospective observational study included all patients with acute urticaria who visited the angioedema reference center of Parisian Academic Public Hospitals – Saint-Antoine in Paris between January 2015 and June 2017. This is a teaching hospital and was accredited by the French Ministry of Health with the objective of improving access to diagnosis and therapy for patients with angioedema (histaminergic and bradykinin-mediated angioedema). The study included only adult patients with a confirmed diagnosis of acute urticaria.

Our study complied with Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.⁷ The protocol was approved by the local ethics committee (Comité de Protection des Personnes). According to French legislation, no written informed consent was required.

Participant inclusion and exclusion criteria

The study inclusion criterion was a diagnosis of acute urticaria in an adult (>18 years old) patient who was admitted to the reference center. The urticaria was spontaneous or inducible urticaria. Wheals could be associated with angioedema. Exclusion criteria were a diagnosis of isolated angioedema without wheals, acute hives with anaphylaxis, bradykinin angioedema, corticosteroid administration in the 5 days previous to visiting the reference center, oral antihistamines in the 5 days previous to visiting the reference center, other treatment for urticaria (omalizumab, montelukast, ciclosporin A), chronic urticaria before acute urticaria diagnosis and other skin diseases (atopic dermatitis, eczema, bullous pemphigoid and acute exanthematous pustulosis). The patients were identified using the reference center database.

Data collection

A trained physician (chart extraction) in the diagnosis of urticaria (acute and chronic) was in charge of the patients' enrollment. He trained with the 10 previous records to the study period. He collected the data, not knowing about the aim of this work. We reviewed all urticaria patient records. For each reference center visit, the physician collected the following data on standardized forms: (i) demographic (age, sex, co-existing conditions); (ii) clinical (possible trigger of acute urticaria, wheal and edema site, presence of itch); and (iii) treatment (antihistamines, corticosteroids). Collection and data were blind to the tested hypothesis. The physician who analyzed charts and principal investigator met monthly to resolve disagreement. The principal investigator (N. J.) double-checked the database.

Definitions and classification

Acute urticaria was defined as the occurrence of spontaneous wheals, angioedema or both for less than 6 weeks. Chronic urticaria was defined on its duration of more than 6 weeks.

Urticaria was classified as spontaneous (no eliciting factor involved) or inducible (specific eliciting factor involved).

Outcomes

The primary outcome was the relapse at day 7 and secondary outcome was relapse at week 6.

Statistical analysis

Data were expressed as mean (standard deviation) for normally distributed variables and as numbers and percentages for categorical variables. To compare the baseline characteristics between patients with and without corticosteroid treatment, we used the χ^2 -test or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables.

Variables associated with relapses were identified using a logistic regression model. A stepwise multivariate analysis was performed with age, sex and corticosteroid administration as candidate variables. All tests were two-sided. $P < 0.05$ was considered statistically significant. We used R statistical software version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

From January 2015 through June 2017, 881 patients visited the reference center for bradykinin-mediated angioedema because of angioedema. Six-hundred and eighty-five out of 881 had angioedema without wheals (Fig. 1). Twelve (6%) out of the 196 (22%) patients who had wheals were excluded from the study because they were receiving epinephrine use for anaphylaxis. Hence, 184 patients with a first episode of acute urticaria were included in the study. The main demographic and clinical characteristics of the patients are provided in Table 1. Most of the patients were female (66%) with a mean age of 42 ± 16 years. Contributing factors could be identified in 65 (35%) cases. In 82 of the 184 patients (45%), corticosteroid treatment was not used. Corticosteroid administration for treatment of acute urticaria was used in 102 (55%) patients. Corticosteroid administration was used in 87 of the 102 patients who had an edema (85%) and in 12 of the 102 patients who had laryngeal edema (12%). Antihistamines were used in 167 (91%) cases without significant difference between the two groups with or without corticosteroids and without significant difference between the two groups with or without relapses. The prevalence of food contributing factors was higher among the patients with corticosteroid administration than among the patients without corticosteroid treatment (5% vs 8%, $P = 0.03$). Doctors who treated initially acute urticaria were 72 general practitioners (with 33 [46%] corticosteroids), 82 emergency physicians (with 56 [68%] corticosteroids), 16 internal physicians (with six [38%] corticosteroids) and 14 dermatologists (with seven [50%] corticosteroids).

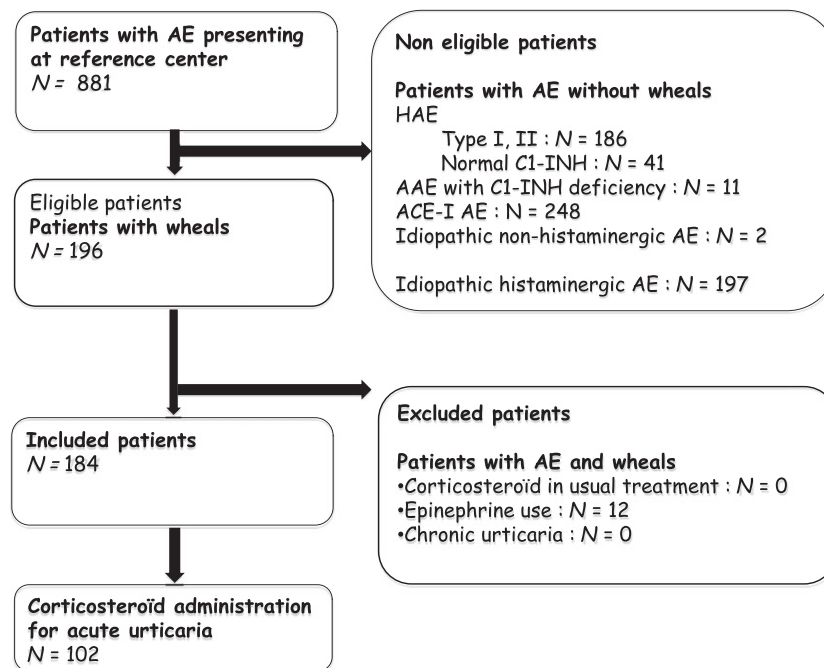


Figure 1. Flowchart of patients study. ACE-I, antagonism converting enzyme-inhibitor; AE, angioedema; HAE, hereditary angioedema.

Table 1. Demographic and clinical characteristics of the study patients

Characteristic	All patients (n = 184)	Corticosteroid (n = 102)	No corticosteroid (n = 82)	P
Age, years (mean $\pm$ SD)	42 $\pm$ 16	41 $\pm$ 16	43 $\pm$ 16	0.88
Male sex, n (%)	62 (34)	32 (31)	30 (37)	0.56
Female sex, n (%)	122 (66)	70 (69)	52 (63)	0.56
Co-existing conditions, n (%)				
Hypertension	30 (16)	13 (13)	17 (21)	0.14
Tobacco	41 (22)	26 (25)	15 (18)	0.24
Allergic rhinitis	47 (26)	28 (27)	19 (23)	0.51
Thyroid diseases	16 (9)	10 (10)	6 (7)	0.55
Estrogen pills	38 (21)	21 (21)	17 (21)	0.98
Asthma	16 (9)	7 (7)	9 (11)	0.32
Atopic dermatitis	10 (5)	4 (4)	6 (7)	0.31
Edema, n (%)	145 (79)	87 (85)	58 (71)	0.02
Larynx	14 (8)	12 (12)	2 (2)	0.01
Tongue	35 (19)	24 (23)	11 (13)	0.08
Uvula	1 (0.05)	1 (1)	0 (0)	0.37
Lips	72 (39)	39 (38)	33 (40)	0.78
Cheeks	50 (27)	25 (24)	25 (30)	0.36
Eyelids	37 (20)	21 (21)	16 (19)	0.86
Itch, n (%)	158 (86)	86 (84)	72 (88)	0.50
Contributing factors, n (%)				
Drugs	65 (35)	38 (37)	27 (33)	0.54
Food	18 (10)	12 (12)	6 (7)	0.3
Infection	9 (5)	8 (8)	1 (1)	0.03
Insect bite	2 (1)	2 (1)	0 (0)	0.20
Contact (e.g. latex, water)	2 (1)	1 (1)	1 (1)	0.88
Stress	15 (8)	7 (7)	8 (10)	0.48
Antihistamines	20 (11)	9 (9)	11 (13)	0.32
Antihistamines	167 (91)	90 (88)	77 (94)	0.19

There were no missing data. SD, standard deviation.

Relapses

Overall, 85 (46%) patients had relapses after less than 7 days (Table 2) whereas 168 (91%) patients had relapses after more than 6 weeks (Table 3). In univariate analysis (Tables 2,3), the rate of corticosteroid administration was significantly higher in cases of relapse after less than 7 days. The dose of antihistamines was not significantly different in groups with or without relapses after less than 7 days. No difference in relapse rates after more than 6 weeks appeared. In the multivariate analysis, the independent factor associated with relapses after less than 7 days was the administration of corticosteroid as treatment of acute urticaria (odds ratio [OR], 1.93; 95% confidence interval [CI], 1.06–3.57; $P = 0.03$) (Table 4).

Long-term follow up

Median follow up was 26 months (range, 17–33). Urticaria was persistent in 122 (66%) patients at this term. Treatment was administrated in 80 (44%) patients during this period. Antihistamines were used in 73 (40%) patients, montelukast in eight (4%), omalizumab in nine (5%) and cyclosporin in four (2%). Seventeen (9%) patients with relapses took corticosteroids intermittently during the recurrences.

Table 2. Factors associated with relapse after less than 7 days in univariate analysis

Characteristic	Relapse <7 days (<i>n</i> = 85)	No relapse <7 days (<i>n</i> = 99)	<i>P</i>
Age, years (mean $\pm$ SD)	42 $\pm$ 15	46 $\pm$ 16	0.08
Male sex, <i>n</i> (%)	32 (38)	30 (30)	0.29
Female sex, <i>n</i> (%)	53 (62)	69 (70)	0.29
Co-existing conditions, <i>n</i> (%)			
Hypertension	14 (16)	16 (16)	0.95
Tobacco	18 (21)	23 (23)	0.74
Atopic	26 (31)	21 (21)	0.15
Thyroid diseases	7 (8)	9 (9)	0.84
Estrogen pills	17 (20)	21 (21)	0.84
Edema, <i>n</i> (%)	64 (75)	81 (82)	0.28
Larynx	8 (9)	6 (6)	0.39
Tongue	17 (20)	18 (18)	0.75
Uvula	0 (0)	1 (1)	0.35
Lips	38 (45)	34 (34)	0.15
Cheeks	18 (21)	18 (18)	0.61
Eyelids	20 (23)	17 (17)	0.28
Itch, <i>n</i> (%)	76 (89)	82 (83)	0.20
Contributing factors, <i>n</i> (%)	30 (35)	35 (35)	0.99
Drugs	11 (13)	7 (7)	0.18
Food	4 (5)	5 (5)	0.91
Infection	0 (0)	2 (2)	0.19
Insect bite	0 (0)	2 (2)	0.19
Contact (e.g. latex, water)	8 (9)	7 (7)	0.56
Stress	10 (12)	10 (10)	0.72
Others	0 (0)	2 (2)	0.19
Antihistamines	80 (94)	87 (88)	0.14
Corticosteroid administration	54 (63)	48 (48)	0.04

There were no missing data. SD, standard deviation.

DISCUSSION

In our study of 184 patients with acute urticaria visits, steroid use was significantly associated with relapses after less than 7 days. Indeed, our OR indicated that risk of relapse after less than 7 days was almost two times higher in patients with acute urticaria treated with than without steroid treatment.

In our study, the overall prevalence of corticosteroid administration for treatment of acute urticaria was high and was similar to a US retrospective observational study (55% vs 48%).⁵ These rates were lower than reported in an Italian retrospective observational study (93%) of 459 patients with acute urticaria prompting emergency department admission.⁸ There is no evident explanation for this discrepancy with the Italian study, especially as our study had a larger proportion of angioedema (79% vs 30%) and the US study had a larger proportion of anaphylaxis (18% vs 6%).^{5,8} In univariate analysis of our study, presence of angioedema, especially that of the larynx, was associated with corticosteroid administration while the efficacy of steroids has not been established in studies with a high level of evidence.^{2,3} In the US study, the large proportion of anaphylaxis (18%) could explain the use of glucocorticoids because steroids remain in use for anaphylaxis because they potentially prevent biphasic anaphylaxis.^{9,10} However, there is no relevant evidence for the use of glucocorticoids in the treatment of an acute episode of anaphylaxis.¹¹

Our main result showed that the independent risk factor for relapse after less than 7 days was corticosteroid administration. In contrast, two previous studies showed that a short burst of corticosteroid treatment in addition to antihistamine could be beneficial to patients with acute urticaria.^{2,3} In a first prospective, randomized, double-blind, placebo-controlled study, the addition of 4-burst prednisone (40 mg/day) to traditional therapy with hydroxyzine (100 mg/day) improved both the efficacy (evaluated by marking an itch score on a 10-cm, 10-point visual analog scale) and time course of resolution of acute urticaria.² In this study, final follow up was only 5 days. In a second non-randomized, non-double-blind, non-placebo-controlled study of 109 patients with acute urticaria, symptoms resolved earlier with prednisone (50 mg/day for 3 days) than with loratadine (10 mg/day for 3 days).³ A recent prospective, randomized, double-blind, controlled trial showed that the addition of a prednisone burst (40 mg p.o. once daily for 4 days) did not improve the symptomatic and clinical response of acute urticaria to levocetirizine among 100 patients.⁴ This study did not support the addition of corticosteroid to H₁ antihistamine as first-line treatment of acute urticaria without angioedema although relapses were not significantly lower in the placebo group (24% of 50 patients) than the prednisone group (30% of 50 patients) (Δ 6%; 95% CI, –11–23%).⁴ The principal limitations of this study were unusual primary endpoint (itching relief 2 days after the emergency department visit, defined as a numeric rating scale score equal to 0–10) because the Urticaria Activity Score over 7 days was not used, and lack of long-term follow up.¹

Finally, in our study, 122 (66%) patients remained symptomatic during the long-term follow up and required long-term

Table 3. Associated factors with relapse after more than 6 weeks in univariate analysis

Characteristic	No relapse >6 weeks (<i>n</i> = 16)	Relapse >6 weeks (<i>n</i> = 168)	<i>P</i>
Age, years (mean ± SD)	47 ± 21	43 ± 15	0.52
Male sex, <i>n</i> (%)	7 (44)	55 (33)	0.79
Female sex, <i>n</i> (%)	9 (56)	113 (67)	0.79
Corticosteroid	11 (69)	91 (54)	0.31
Co-existing conditions, <i>n</i> (%)			
Hypertension	4 (25)	26 (15)	0.32
Tobacco	5 (31)	36 (21)	0.36
Allergic rhinitis	4 (25)	43 (26)	0.96
Thyroid diseases	1 (6)	15 (9)	0.72
Estrogen pills	3 (19)	35 (21)	0.84
Edema, <i>n</i> (%)	13 (81)	132 (79)	0.80
Larynx	3 (19)	11 (6)	0.08
Tongue	2 (12)	33 (20)	0.49
Uvula	0 (0)	1 (0.6)	0.76
Lips	7 (44)	65 (39)	0.69
Cheeks	5 (31)	41 (24)	0.55
Eyelids	1 (6)	36 (21)	0.15
Itch, <i>n</i> (%)	14 (87)	144 (86)	0.84
Contributing factors, <i>n</i> (%)	7 (44)	58 (34)	0.46
Drugs	3 (19)	15 (9)	0.21
Food	2 (12)	7 (4)	0.14
Infection	0 (0)	2 (1)	0.66
Insect bite	0 (0)	2 (1)	0.66
Contact (e.g. latex, water)	3 (19)	12 (7)	0.10
Stress	1 (6)	19 (11)	0.53
Others	0 (0)	2 (1)	0.66
Antihistamines	13 (81)	154 (92)	0.17

There were no missing data. SD, standard deviation.

Table 4. Multivariate logistic regression analysis of factors associated with relapses after less than 7 days

	OR (95% CI)	<i>P</i>
Age	0.99 (0.97–1.00)	0.14
Contributing factors (drugs)	1.85 (0.66–5.51)	0.25
Antihistamines	2.58 (0.89–8.67)	0.10
Corticosteroid administration	1.93 (1.06–3.57)	0.03

CI, confidence interval; OR, odds ratio.

treatment. All treatments were used in accordance with consensus guidelines.^{1,12–14}

Our study had several limitations. This was a retrospective and observational study which was not designed to show a causal link. Even though data collection was standardized with follow up of primary outcome measured clinically (and not by telephone), some factors, such as dose and duration of treatment, were not documented. Nevertheless, the high number of included patients and the selected population characterized in a reference center strengthens the result of our study.

In conclusion, the prevalence of corticosteroid administration in patients with acute urticaria visiting our angioedema center was high. This prevalence was even higher when angioedema was associated with urticaria. In our retrospective

observational study, corticosteroid administration was an independent risk factor associated with relapses after less than 7 days. A prospective randomized controlled powered well-designed trial is needed to demonstrate the non-inferiority of efficacy of an antihistamine alone in comparison with an association of antihistamine and corticosteroid in the treatment of acute urticaria.

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CONFLICT OF INTEREST: None declared.

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