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Title: **H1-antihistamines reduce progression to anaphylaxis among emergency department patients with allergic reactions**

Author list

T. Kawano, MD, PhD[12]; F.X. Scheuermeyer, MD MHSc[13]; K. Gibo, MD[67]; R. Stenstrom, MD, PhD[1345]; B Rowe MD MSc[8]; E. Grafstein MD[135]; B. Grunau, MD MHSc [1345]

Affiliations

[1] The Department of Emergency Medicine, St. Paul's Hospital, Vancouver, BC, Canada

[2] The Department of Emergency Medicine, University of Fukui Hospital, Fukui Prefecture, Japan

3 The Department of Emergency Medicine, University of British Columbia, Vancouver, BC, Canada.

[4] The School of Population and Public health, University of British Columbia, Vancouver, BC, Canada.

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[5] The Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, Canada

[6] Okinawa Prefectural Chubu Hospital, Department of Emergency Medicine, Okinawa, Japan

[7] Biostatistics Center, Kurume University, Kurume, Fukuoka, Japan.

[8] The Department of Emergency Medicine and the School of Public Health, University of Alberta, Edmonton, AB, Canada

Corresponding author: Dr. Takahisa Kawano, Department of Emergency Medicine, St. Paul's Hospital, 1081 Burrard Street, Vancouver, BC, Canada

Email address: Takahisa.Kawano@ubc.ca

Telephone: +1-(604)806-8480

Fax number: +1-(604)806-8488

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Abstract (280 words; word limit, 500 words)

Objectives: H1-antihistamines (H1a) can be used to treat ED patients with allergic reactions; however, this is inconsistently done, likely as there is no evidence that this therapy has an impact on serious outcomes. Among emergency department (ED) patients initially presenting with allergic reactions, we investigated whether H1a were associated with lower rates of progression to anaphylaxis.

Methods: This was a retrospective cohort study conducted at two urban Canadian EDs from April 1, 2007 to March 31, 2012. We included consecutive adult patients with allergic reactions while excluding those presenting with anaphylaxis, according to pre-specified criteria. The primary outcome was the proportion of patients who subsequently developed anaphylaxis during medical care, either by emergency medical services (EMS) or in the ED. A pre-specified subgroup analysis excluded patients who received H1a prior to EMS or ED contact. We compared those who received H1a and those who did not, and used multivariable regression and propensity score adjustment techniques to compare outcomes.

Results: Of 2,376 overall patients included, 1,880 (79.1%) were managed with H1a. Of the latter group, 36 / 1,880 (1.9%) developed anaphylaxis, compared to 17 / 496 (3.4%) in the non-H1a-treated group (adjusted odds ratio [AOR] 0.34, 95% CI 0.17 to 0.70; number needed to treat [NNT] to benefit 44.74, 95% CI 35.36 to 99.67). In the subgroup analysis of 1,717 patients who did not receive H1a prior to EMS or ED contact, a similar association was observed (AOR 0.26, 95% CI 0.10 to 0.50; NNT to benefit 38.20, 95% CI 32.58 to 55.24).

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Conclusions: Among ED patient with allergic reactions, H1a administration was associated with a lower likelihood of progression to anaphylaxis. These data indicate that early H1a treatment in the ED or prehospital setting may decrease progression to anaphylaxis.

Keywords: Allergic reactions, Anaphylaxis, prevention, emergency department.

Introduction

H1-antihistamines (H1a) are inverse agonists that combine with the H1-receptor to shift the latter to its regular inactive state. [1] H1a's have been used prior to administration of radiographic contrast media or immune therapies in patients at high risk for anaphylaxis. [2-4] However, evidence supporting H1a use in the emergency department is limited to symptomatic improvement of pruritus and urticaria. [5,6] While the majority of emergency physicians use H1a in the treatment of anaphylaxis, [7-9] administration of anti-histamines in those with allergic reactions is less consistent with 28 % to 38% of allergic patients not receiving this therapy in the ED, [8-10] likely due to a lack of data indicating acute benefit. [8,10,11]

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death, [12] thus data investigating potential therapies to prevent progression of allergic reactions to anaphylaxis is crucial. [13,14] However, current available recommendations for anaphylaxis prevention have focused on long-term management, based on expert

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opinion and consensus. [15] Among the 1.03 million patients who visit EDs in the U.S annually with allergic reactions, [8] the benefit of H1a treatment remains unclear.

Among a cohort of ED patients with allergic reactions, we sought to determine whether those who were treated with H1a had a lower occurrence of subsequent anaphylaxis.

Methods

Design and Setting: This was a sub-study of a retrospective cohort at two urban EDs in Canada from April 1, 2007 to March 31, 2012 (details have been described previously [7,16]). Both sites are academic teaching hospitals in Vancouver, British Columbia, Canada, affiliated with the University of British Columbia. St. Paul's Hospital is a tertiary care center with an annual census of approximately 70 000 during the study period, while Mount St. Joseph's Hospital is an affiliated community center that had approximately 25 000 annual ED visits. The comprehensive electronic medical record (EMR) and order entry system were shared by two hospitals, and recorded the following: date and time of all arrivals, all demographics, diagnostic investigations and their results, medical treatments and their timing, consultations and their timing, as well as the time of admission or discharge. The institutional review boards and affiliated ethics committees of Providence Health Care, the University of British Columbia, and Vancouver Coastal Health approved the study protocol.

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Interventions: Emergency physicians managed patients with allergic reactions as per their individual discretion; available pharmacological therapies included H1a (diphenhydramine), H2-antihistamines, steroids, and epinephrine. Emergency medical service (EMS) paramedics managed patients based on clinical judgment and could provide diphenhydramine (the only available H1a) at 50 mg intravenously. They were also permitted to administer epinephrine up to 0.3 mg intramuscularly, or as an infusion at 2-10 micrograms / min if they had advanced life-support training.

Patient selection: At both sites, emergency physicians are required to complete a discharge summary with diagnostic codes. We identified all patients with an ED diagnostic code of "allergic reaction" (ICD 9 code 995.3), which was the only available allergy-related code in the EMR. We excluded those who met the pre-specified definition of anaphylaxis at first evaluation by either EMS personnel (if EMS-treated) or ED staff. The definition of anaphylaxis was adapted from the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network criteria (**Box 1**) and has been described previously. [7,12,16] Further exclusions were patients younger than 17 years, those with a primary diagnosis of asthma, these who left before assessment by a nurse or a physician, those whose suspected allergen was an angiotensin-converting enzyme inhibitor, and those who had a past history of non-allergic angioedema.

Measurements: As previously described, [7,16] three investigators – two medical students and one ED faculty physician– systematically reviewed all index and follow-up encounters after training on a set of randomly selected 50 records. Standard criteria for chart reviews were followed [17,18] with weekly meetings to review data collection and

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resolve disputes. Abstractors were unaware of this sub-study hypothesis. Charts with conflicting data prompted adjudication using two independent reviewers to reach consensus.

Data were abstracted onto a standardized spreadsheet (Microsoft Excel 2011, Microsoft Corp., Redmond, WA) and included the followings: patient demographics and past medical history, characteristics of presentation, EMS and ED treatments, prespecified outcomes, post discharge subsequent visits, and the location of H1a administration (prior to EMS or ED contact, by EMS, or in the ED). An additional investigator (T.K.) collected the time of H1a administration, epinephrine and steroid, and the time of anaphylaxis to determine whether H1a were administered before and after developing anaphylaxis. We assessed the reliability of these additional data with a secondary review for the time of H1a administration and anaphylaxis (where applicable) by two emergency physicians (BEG and RS, who were blinded to the first assessment) of 5% randomly selected study patients.

Outcomes: The primary outcome was the proportion of patients who subsequently developed anaphylaxis either during transportation or during the ED visit. Further outcomes of interest included the number of patients with severe anaphylaxis (see Box 1) [19] or biphasic reactions during observation (see Box 1) [7,16], the number who were admitted to hospital, median ED length of stay (LOS), and median time to anaphylaxis. H1a are known to have potentially adverse effects on patients including decreased level of consciousness, QT prolongation, and hypotension. [20-23] While it is difficult to ascertain whether signs of hypotension or alterations of consciousness are due to the disease process or the treatment, if study patients (none of whom initially had anaphylaxis at the point of first medical care) developed neurological symptoms or blood pressure

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lower than 90 mmHg, they satisfied our criteria for severe anaphylaxis (Box 1) and were compared between H1a-treated and untreated groups. The definition of "time to anaphylaxis" was the length of time between the first patient contact (with EMS or ED) and the onset of anaphylaxis (if applicable). Using each patient's unique provincial health number, the regional database were interrogated to identify patients who re-presented to an ED with anaphylaxis within 7 days, and the provincial vital statistics database were cross-referenced to determine mortality during the same time frame.

Statistical Analysis: First, we assessed the interrater reliability measures of the secondary review by calculating kappa values. Next, eligible participants were dichotomized by H1a administration: the H1a-treated group was defined as patients who received H1a at any location—either prior to EMS contact, via EMS, or in the ED. However, if patients only received H1a after they met the criteria of anaphylaxis, they were classified into the non-H1a treated group. Missing data on vital signs were addressed by multiple imputation, (mice 2.2.5 package in R version 3.2.4, Foundation for Statistical Computing, Vienna, Austria) [24] and estimates with standard errors across 50 imputed data sets were combined with a standard approach. [25] In addition, as a sensitivity analysis we conducted a separate "complete case analysis" which only included cases with complete data. [26,27] Dichotomous variables were presented as percentages and 95% confidence intervals (95% CI) and non-normally distributed continuous variables as medians and interquartile ranges (IQR). Where appropriate, we conducted Mann-Whitney U, Fisher's exact or chi square tests to test unadjusted association of variables and further outcomes between two groups.

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Primary analysis

We conducted a multivariate logistic regression (simultaneous method) to compare the probability of subsequent anaphylaxis between patients who were administered H1a and those who were not. This model provides an estimate of the odds ratio by approximating the relative risk due to estimated rare disease assumption. [28] We controlled for potential confounders based on biological plausibility, including age, gender, prior allergies or asthma, precipitant (drug, food, others, or unknown), ambulance arrival, vital signs at first evaluation, (systolic blood pressure, [BP], respiratory rate, and oxygen saturation [SpO_2]), symptoms at first evaluation (dyspnea, or skin, or mucosal involvement) and concomitant treatments (epinephrine and/or steroid before the development to anaphylaxis). To meet the assumption of linearity in the logit for continuous variables, we conducted model selection based on AIC after smoothing the variable of age using linear spline (k=3) and categorizing the following variables: systolic blood pressure (SBP), respiratory rate (RR) and SpO2 based on clinical cut off value for an abnormality (SBP; < 100 mg or >= 100 mg, RR; < 12, 12 to 24, >24, and SpO2; <90% or >=90%). [29,30] After this selection, we decided to use age and SpO2 as continuous variables and SBP and RR as categorical variables. As our outcomes were estimated to be rare (probably under 4.0 %; there was no available data reporting the incidence of subsequent anaphylaxis), our model would be potentially overfitting as we included all listed predictors in our model to evaluate our clinical hypothesis. [31,32] However, we were not able to narrow down the appropriate number of potential confounding variables based on subject-matter knowledge due to a lack of previous research. To evaluate the issue of overfitting, optimism of each model was evaluated. [30] Subsequently in subgroup analysis, to overcome this issue, we applied propensity score methods to reduce number of predictors, which summarize score on relationship

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between H1a use and the potential confounders. [33] A propensity score was not possible for this cohort as it included those who self-administered anti-histamines before other cofounders were observed. [34] The number needed to treat (NNT) of H1a was calculated as the inverse value of the adjusted absolute risk reduction assessed by regression risk analysis. [35,36] This regression risk analysis is able to estimate an accurate adjusted absolute risk reduction from multiple regression models. [35,36] Finally, to assess overall model performance, we conducted Hosmer-Lemeshow test and omnibus chi square for goodness-of-fit. A p-value of less than 0.05 was considered as statistically significant.

Subgroup analysis

It is possible that clinicians were more likely to administer H1a to patients with certain characteristics, which may have biased our model estimating the effect of H1a on the development of anaphylaxis. Therefore, after excluding the group of patients who had used H1a prior to EMS or ED contact, we analyzed the remaining patients with two methods: (1) a multivariable logistic regression with adjustment for the same confounders as the main analysis, and (2) a propensity score adjusted logistic regression, where H1a administration, and propensity score were treated as independent variables, where propensity score could reduce the effects of confounders and selection bias. [34] The propensity score was calculated by the regression of H1a administration on the potential confounders, excluding the variables of epinephrine and/or steroids use as these variables were administered after and/or at the same time of H1a administration. This propensity score adjustment methods also could reduce number of predictors, summarizing one variable on association between H1a use and other confounders and reducing the potential probability of overfitting. [33]

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Results

During the study period, 2,376 eligible patients with a discharge diagnosis of "allergic reaction" were identified, with 1880 (79.1%) treated with H1a (**Figure 1**). The interrater reliability measures (kappa) of the secondary review were as follows: time of anaphylaxis, 0.84 (95% CI 0.64 to 0.95), and time of H1a administration, 1.00 (95% CI 0.89 to 1.00). Thirteen patients (0.6%) did not have a provincial health number and follow-up visits and mortality were not available.

Table 1 summarizes baseline demographics. Patients treated with H1a were younger and were more likely to have past history of asthma and allergies, be transported by ambulance, have a food precipitant, report dyspnea, and have skin or mucosal involvement. H1a-treated patients were also more likely to receive epinephrine and steroids.

Overall, 53 / 2376 (2.2%) patients developed subsequent anaphylaxis, with 36 / 1880 (1.9%; 1.3% - 2.7%) in the H1a-treated group and 17 / 496 (3.4%; 2.0% - 5.5%) in the untreated group (**Table 1**). There was no significant unadjusted difference in proportion of severe anaphylaxis, admission, time to anaphylaxis, re-visits for anaphylaxis or mortality between two groups.

The primary analysis is presented in **Table 2**. Our logistic regression on multiple imputed datasets demonstrates that H1a administration was associated with decreased probability of subsequent anaphylaxis (adjusted odds ratio [AOR] 0.34, 95% CI 0.17 to

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0.71; number needed to treat [NNT] to benefit 44.74, 95% CI 35.36 to 99.67). Epinephrine used was associated with an increased probability of subsequent anaphylaxis whilst steroid administration was associated with a decreased probability of anaphylaxis despite non-statistical significance (**Table 3**). The optimism and the goodness-of-fit in each model were shown in **supplemental table**.

Our secondary analysis compared outcomes for the subgroup of patients who did not receive H1a prior to EMS or ED contact. The H1a group had 17/1,221 (1.4%; 0.8% to 2.2%) cases with subsequent anaphylaxis, in comparison to 17/496 (3.4%; 2.0% - 5.5%) in the non-treated group. In our multiple logistic regression on multiple imputed datasets, patients who received H1a after first evaluation were less likely to develop subsequent anaphylaxis (AOR 0.26, 95% CI 0.10 to 0.50; NNT to benefit 38.20, 95% CI 32.58 to 59.24, **Table 2 and 3**). The propensity score adjusted model yielded a similar result (AOR 0.24, 95% CI 0.11 to 0.49; NNT to benefit 38.20, 95% CI 32.86 to 58.63, **Table 2**).

As a sensitivity analysis, we also conducted the first and secondary analysis in completed case data, which showed similar results in multiple imputed datasets (**Table 2**).

Discussion

We examined a cohort study of 2,376 consecutive emergency department patients with allergic reactions, of whom 2.2% developed subsequent anaphylaxis. We found that

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those who received H1a—either self-administered, or given by medical personnel—were less likely to develop a subsequent anaphylactic reaction during observation. This association was consistent in a subgroup of patients who did not receive H1a prior to EMS or ED contact and in our propensity-adjusted analysis (that accounted for potential selection bias stemming from non-random H1a administration). These results demonstrate to clinicians that treating allergic reactions early with H1a—either in the prehospital or the ED setting—may decrease progression to anaphylaxis. This may also assist systems of care by placing emphasis in on early antihistamine administration that may be initiated by EMS or nursing-initiated protocols upon arrival in the ED.

Two small previous ED-based studies have evaluated H1a in patients with allergic reactions or anaphylaxis. In a trial of 91 patients randomized to either diphenhydramine or diphenhydramine and ranitidine, urticaria was improved in the latter group with no differences in angioedema or hypotension. [5] Of 36 patients randomized to cimetidine, diphenhydramine, or a combination of the two, diphenhydramine improved symptoms. [6] No ED based studies have demonstrated that H1a are helpful in preventing progression to anaphylaxis. [37].

Several studies in non-ED settings have examined the effectiveness of prophylactic H1a administration in asymptomatic patients to reduce the risk of allergic reactions prior to potential allergen exposure. These findings have been inconsistent, likely due to differences in study settings, numbers, design, and outcomes. [4,38,39] It is important to

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recognize that these findings have not been reported in ED patients, or in patients with an active allergic reaction.

We found that epinephrine use was associated with development of anaphylaxis during the ED stay. This likely represents clinicians astutely recognizing a patient with the potential to progress in level of acuity. There is no robust evidence demonstrating efficacy of epinephrine in anaphylaxis;[40] however, this is widely accepted to be the case. In order to account for the potentially beneficial effect of epinephrine on the progression to anaphylaxis, we included this variable in our adjusted regression models; despite this, the benefit of H1a remained statistically significant. We also accounted for the potential effect of steroid administration in our models; although there was no statistically significant association of steroid use and decreased progression to anaphylaxis in our primary analysis, there was a trend suggesting this. Further research on the potential benefit of steroid administration in ED patients with allergic-related presentations is needed.

Although H1a are generally considered to be safe, possible adverse cardiovascular effects have been acknowledged, [41] including potential for hypotension, which may worsen symptoms of anaphylactic shock. [23] In our study, we did not find a difference in the proportion of patients with anaphylaxis and hypotension, severe anaphylaxis, admission rate, or mortality between H1a treated and non-treated patients. There is likely sufficient evidence support to the safety of H1a administration to patients at risk for anaphylaxis.

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In this study, 79% of patients with allergic reactions were treated with H1a, which is higher than the prescription rate in previous reports. [8-10] The reason behind this variation is unclear, but may be due to local practices of care. The evidence base supporting the use of anti-histamines for those with allergic reactions is weak, [37] and thus it is not surprising that variations in care may occur. In this context, our findings could encourage ED physicians to administer H1a to patients with allergic reaction more frequently by providing potential benefits for preventing progression to anaphylaxis.

Limitations

Several limitations are noteworthy. First, the study sites did not have a predefined protocol for acute allergy; practice patterns and results may differ elsewhere. Second, patients were identified by a diagnostic code of "allergic reaction," which may potentially overlap with similar codes such as "asthma" or "rash". Third, this is a retrospective chart review study, where undocumented and/or unmeasured variables are possible; however, data were collected by the robust methods. [17,18] Fourth, while it is possible that H1a administration delays rather than prevents progression to anaphylaxis, we found that there was no significant difference in the percentage of ED revisits for anaphylaxis after discharge. Fifth, it is possible that our logistic regression model was affected by patients within our cohort who presented on more than one occasion, as this may have affected the independence of individual observations. In addition, even propensity score adjustment has a possibility that its estimate may be still biased if certain covariates are excluded. Our estimates in multiple logistic regression models also may be limited due to the issue of overfitting. Finally, we did not

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classify H1a into intravenous or oral administration routes as these may have different extent of side effects and onset. [42-44]

Conclusion

Among ED patient with allergic reactions, H1a administration was associated with a lower likelihood of progression to anaphylaxis. These data indicate that early H1a treatment in the ED or prehospital setting may decrease progression to anaphylaxis.

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FIGURE LEGENDS

Box 1. Definition of anaphylaxis, severe case of anaphylaxis and biphasic reaction

Figure 1. Patient recruitment diagram

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Table 1. Patient demographics and outcomes of 2,376 patients with allergic reactions managed at two emergency departments in Canada.

	H1-antihistamine treated group (n = 1880)		Non treated group (n=496)	
Characteristics	n or Median (IQR or %)	Missing (%)	n or Median (IQR or %)	Missing (%)
Age (IQR)	34 (26 - 47)		39 (28 - 54)	
Male sex (%)	703 (37.4)		188 (37.9)	
History of allergy (%)	1165 (62.0)		219 (44.2)	
History of asthma (%)	244 (13.0)		35 (7.1)	
Known/suspected precipitant				
Drug (1/0) (%)	474 (25.2)		180 (36.3)	
Food (1/0) (%)	687 (36.5)		73 (14.7)	
Other (1/0) (%)	228 (12.1)		95 (19.2)	

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Allergen unknown (%)	491 (26.1)		148 (29.8)	
Ambulance arrival (%)	318 (16.9)		39 (7.9)	
Vital signs and symptoms at the first evaluation				
Systolic blood pressure (IQR), mmHg	129 (117 - 142)	60 (3.2)	127 (114 - 142)	33 (6.7)
Systolic blood pressure group (%)				
<100 mmHg	64 (3.3)	14 (2.8)		
100 mmHg<=	1756 (93.4)	449 (90.5)		
Respiratory rate (IQR), bpm	18 (16 - 20)	98 (5.3)	18 (16 - 18)	39 (7.9)
Respiratory rate group (%)				
<12	23 (1.2)		2 (0.4)	
12-24	1737 (92.4)		453 (91.3)	
24<	22 (1.2)		2 (0.4)	
SpO2 (IQR), %	98 (97 - 99)	99 (5.3)	98 (97 - 99)	58 (11.7)
Skin involvement (%)	1309 (69.6)		322 (64.9)	

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Mucosal tissue involvement (%)	357 (19.0)	46 (9.3)
Dyspnea (%)	260 (13.8)	41 (8.3)
Treatment before the development to anaphylaxis		
Epinephrine (%; 95% CI)	146 (7.8; 6.6 - 9.1)	14 (2.8; 1.6 - 4.7)
Steroid (%; 95% CI)	868 (46.2; 43.9 - 48.5)	77 (15.5; 12.4 - 19.0)
Outcomes		
Subsequent anaphylaxis (%; 95% CI)	36 (1.9; 1.3 - 2.7)	17 (3.4; 2.0 - 5.5)
Biphasic reaction (%; 95% CI)	0 (0; 0 - 0.2)	0 (0; 0 - 0.6)
Severe anaphylaxis (%; 95% CI)	8 (0.4; 0.2 - 0.8)	3 (0.6; 0.1 - 1.8)
Admission (%; 95% CI)	14 (0.7; 0.4 - 1.2)	1 (0.2; <0.1 - 1.1)
LOS (mins, IQR)	107 (73 - 165)	77 (53 - 114)
Time to anaphylaxis (mins, IQR)	48 (27 - 167)	29 (21 - 60)
Revisit for anaphylaxis (%; 95% CI)	9 (0.5; 0.2 - 0.9)	2 (0.4; <0.1 - 1.5)

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Death (%; 95%CI)	0 (0; 0 - 0.2)	0 (0; 0 - 0.6)

H1-antihistamines treated group: patient treated with H1-antihistamines prior to EMS or ED contact, during transportation by EMS or the observation at ED. Abbreviation; EMS: emergency medical service, ED: emergency department, IQR: interquartile range, CI: confidence interval, LOS: length of ED stay.

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Table 2. The H1-antihistamines exposure on the probability of subsequent anaphylaxis in primary and secondary analysis

	Main analysis		Subgroup analysis	
	AOR (95% CI)	NNT to benefit (95% CI)	AOR (95% CI)	NNT to benefit (95% CI)
Multiple imputated analysis				
Unadjusted	0.55 (0.31 to 0.99)	-	0.40 (0.20 to 0.79)	-
Multivariable model	0.34 (0.17 to 0.70)	44.74 (35.36 to 99.67)	0.26 (0.10 to 0.50)	38.20 (32.58 to 59.24)
PS adjusted model	-	-	0.24 (0.11 to 0.49)	38.20 (32.86 to 58.63)
Complete-case analysis				
Unadjusted	0.55 (0.31 to 1.00)	-	0.40 (0.20 to 0.79)	-
Multivariable model	0.34 (0.17 to 0.71)	44.74 (35.32 to 101.51)	0.23 (0.10 to 0.50)	38.20 (32.53 to 59.39)
PS adjusted model	-	-	0.23 (0.11 to 0.47)	38.20 (32.91 to 55.97)

Abbreviation; AOR: adjusted odds ratio. CI: confidence interval, NNT: number needed to treat.

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Table 3. The Odds ratio of covariates on multivariate logistic model in primary and subgroup analysis on multiple imputed models

	Primary analysis	**Subgroup analysis**
Covariates	AOR (95% CI)	AOR (95% CI)
Age	1.02 (1.00 to 1.04)	1.01 (0.99 to 1.03)
Sex, Male vs female	1.44 (0.79 to 2.63)	1.64 (0.77 to 3.51)
History of allergy	1.01 (0.53 to 1.95)	1.24 (0.56 to 2.85)
History of asthma	2.11 (0.93 to 4.44)	3.10 (1.17 to 7.66)
Known/suspected precipitant		
Others	reference	reference
Drug	2.68 (0.82 to 12.20)	1.98 (0.57 to 9.41)
Food	3.51 (1.07 to 16.29)	1.68 (0.44 to 8.38)
Allergen unknown	2.31 (0.67 to 10.95)	1.41 (0.36 to 7.10)
Ambulance arrival	1.14 (0.50 to 2.45)	2.32 (0.91 to 5.55)
Systolic blood pressure		
<100 mmHg	reference	
100 mmHg<=	0.66 (0.22 to 2.61)	0.39 (0.12 to 1.58)
Respiratory rate		
<12 bpm	reference	reference
12-24 bpm	0.33 (0.06 to 6.34)	683709 (0 to 330478)
24 bpm<	2.74 (0.26 to 64.11)	588348 (0 to 372601)
SpO2, per 1 % increase	0.88 (0.74 to 1.07)	0.83 (0.67 to 1.04)

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Skin involvement	3.22 (1.58 to 7.17)	1.91 (0.85 to 4.63)
Mucosal tissue involvement	3.10 (1.57 to 5.97)	4.82 (2.12 to 11.04)
Dyspnea	1.39 (0.60 to 2.94)	1.61 (0.57 to 0.4.06)
Epinephrine	7.51 (3.31 to 16.64)	7.27 (2.24 to 21.88)
Steroid	0.56 (0.28 to 1.08)	0.37 (0.13 to 0.92)

Abbreviation; AOR: adjusted odds ratio. CI: confidence interval.

Anaphylaxis: Any of the following three numbered criteria must be satisfied:

1. Both of the following must be satisfied:
   a. skin or mucosal tissue involvement
   b. one of the following:
      i. Respiratory compromise
      ii, Systolic blood pressure (sBP) < 90 mm Hg or syncope

2. Two of the following must be satisfied after exposure to a "likely" allergen:
   a. Skin or mucosal tissue involvement
   b. Respiratory compromise
   c. sBP < 90 mm Hg or syncope (concurrent to other symptoms)
   d. Gastrointestinal symptoms

3. sBP < 90 mmHg after exposure to a known allergen.

Skin Involvement: Urticaria, rash, pruritus, or swelling of the face or err, Localized pruritus or rash that was deemed the result of trauma or an obvious insect bite was not considered as fulfilling the definition of "skin involvement."

Mucosal tissue involvement: Swelling of lips, tongue or pharynx.

Respiratory compromise: Wheeze or stridor on auscultation, hypoxemia (oxygen saturation < 95%) or respiratory rate > 22 breaths / min.

Gastrointestinal Symptoms: Abdominal pain or vomiting that is present in the ED.

Neurological Symptoms: confusion, collapse, loss of conscious, syncope or incontinence.

Known Allergen: A substance that had previously caused an allergic reaction to the patient.

Likely Allergen: A substance that (1) the patient was exposed to before the development of symptoms+ (2) was deemed the cause of the allergic reaction by the attending physician; and (3) had not previously caused a known reaction.

Severe case of Anaphylaxis : Patients experienced hypotension (sBP<90), oxygen saturation < 92% and/or neurological symptoms during transportation by EMS and/or observation at ED.

Biphasic Reaction: Recurrent or new signs or symptoms occurring during transportation by EMS and/or observation at ED after an initial allergy related presentation that satisfy the definition for anaphylaxis, without any obvious further exposure to an offending allergen.

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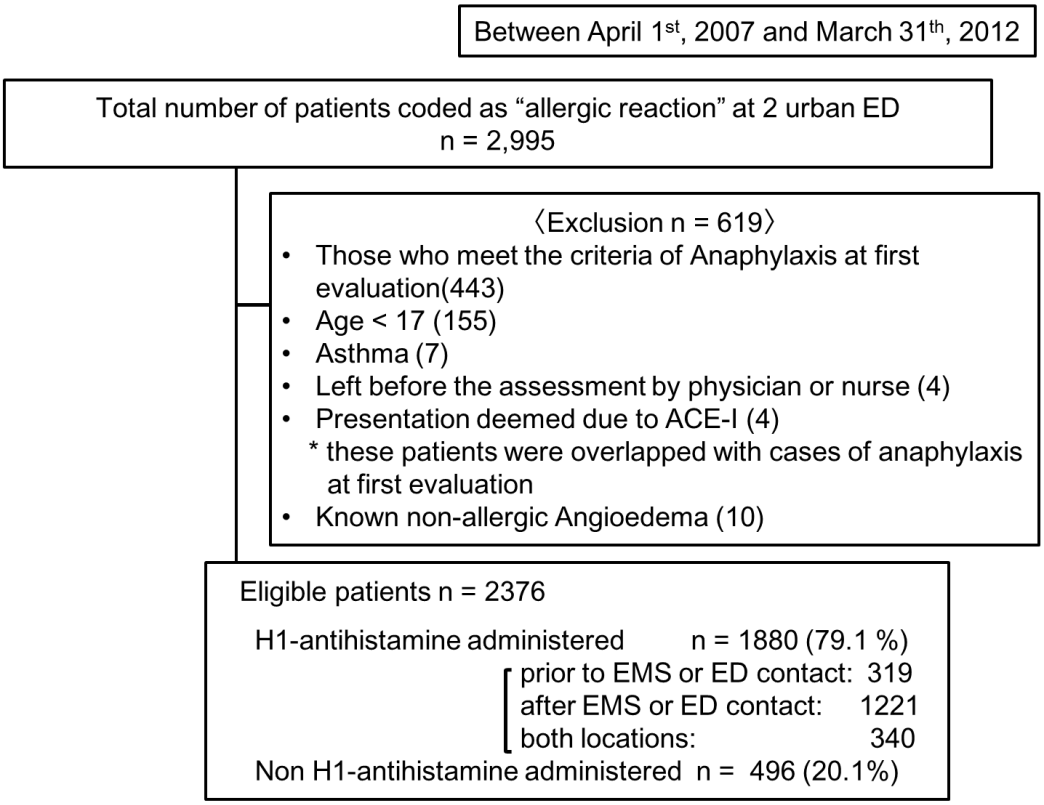

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