

Algorithm for the diagnosis of anaphylaxis and its validation using population-based data on emergency department visits for anaphylaxis in Florida

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Background: Epidemiologic studies of anaphylaxis have been limited by significant underdiagnosis.

Objective: The purpose of this study was to develop and validate a method for capturing previously unidentified anaphylaxis cases by using International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) based datasets.

Methods: Florida emergency department data for the years 2005 and 2006 from the Florida Agency for Health Care Administration were used. Patients with anaphylaxis were identified by using ICD-9-CM codes specifically indicating anaphylaxis or an ICD-9-CM algorithm based on the definition of anaphylaxis proposed at the 2005 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network symposium. Cases ascertained with the algorithm were compared with the traditional case-ascertainment method. Comparisons included demographic and clinical risk factors, proportion of monthly visits, and age/sex-specific rates. Cases ascertained with anaphylaxis ICD-9-CM codes were excluded from those ascertained with the algorithm. **Results:** One thousand one hundred forty-nine patients were identified by using anaphylaxis ICD-9-CM codes, and 1,602 patients were identified with the algorithm. The clinical risk factors and demographics of cases were consistent between the 2 methods. However, the algorithm was more likely to identify older subjects ($P < .0001$), those with hypertension or heart disease ($P < .0001$), and subjects with venom-induced anaphylaxis ($P < .0001$).

Conclusion: This study introduces and validates an ICD-9-CM-based diagnostic algorithm for the diagnosis of anaphylaxis to capture subjects missed by using the ICD-9-CM anaphylaxis codes. Fifty-eight percent of anaphylaxis cases would be missed without the use of the algorithm, including 88% of venom-induced cases. (*J Allergy Clin Immunol* 2010;■■■:■■■-■■■.)

Key words: Anaphylaxis, epidemiology, emergency, International Classification of Disease–Ninth Revision–Clinical Modification, underdiagnosis

Anaphylaxis is an acute generalized allergic reaction that can be life-threatening. This syndrome usually involves more than 1 organ system. Signs and symptoms can include respiratory distress, hypotension, angioedema, urticaria, nausea, vomiting, diarrhea, abdominal/pelvic cramps, tachycardia, and cyanosis. The exception is hypotensive shock without other symptoms in the context of contact with a known or likely allergen.¹ Because of the wide range of symptoms, the diagnosis is often unclear, especially to physicians who are unfamiliar with the syndrome. Unfamiliarity with and misdiagnosis of this multiple-symptom, multiorgan syndrome might play a large part in the underdiagnosis of anaphylaxis.² A few hospital-based studies have demonstrated that underdiagnosis occurs. A 4-month study in a community hospital emergency department (ED) revealed only 4 patients with a diagnosis of anaphylaxis. An additional 13 patients were identified as having anaphylaxis through a review of their medical records. The original diagnosis for these 13 patients was an unspecified allergic reaction.³ The authors concluded that the majority of cases would not have been identified with the anaphylaxis-specific International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

A recent article by Campbell et al⁴ that examined the use of prescription epinephrine further supports the contention that anaphylaxis is commonly underdiagnosed. The study identified 157 cases using the ICD-9-CM codes for anaphylactic shock. An additional 54 cases of anaphylaxis were identified by reviewing a random sample of 600 medical records in which the ICD-9-CM codes indicated an associated diagnosis (food/venom). Finally, recent reviews of Florida death certificate and hospitalization data suggest that some anaphylactic deaths in hospitalized patients reported on death certificates are not recorded in the hospital discharge diagnosis records as such.^{5,6} The underdiagnosis of this syndrome presents a public health risk because proper treatment of anaphylaxis depends on its timely diagnosis, and prevention depends on an accurate understanding of the determinants of the disease.⁷⁻⁹

The objective of this study was to develop and validate a method for capturing previously unidentified anaphylaxis cases from ED discharge data. The authors present an algorithm based on a clinical definition for anaphylaxis proposed at the 2005 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) symposium.¹ The ICD-9-CM codes needed for record review and for the use of

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Abbreviations used

CI:	Confidence Interval
COPD:	Chronic obstructive pulmonary disease
ED:	Emergency department
ICD-9-CM:	International Classification of Disease, Ninth Revision, Clinical Modification
NIAID/FAAN:	National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network

this definition with hospital discharge and ED data are included in the authors' algorithm. This article explores and compares the commonly used ICD-9-CM codes to identify patients with anaphylaxis versus coding based on the NIAID/FAAN-proposed clinical definition in the context of a population-based analysis of ED visits for anaphylaxis in Florida for 2005 through 2006.

METHODS**Source population and inclusion criteria**

Nonfederal ED data for 2005 and 2006 were obtained from the Florida Agency for Health Care Administration. Diagnosis information was coded by using the ICD-9-CM. For each record, the Agency for Health Care Administration allows for the reporting of 1 primary diagnosis, 9 secondary diagnoses (a total of 10 diagnosis fields), and 3 external cause-of-injury codes.

Anaphylaxis cases were defined in one of 2 ways. Method I identified patients who had an ICD-9-CM code specific to anaphylaxis within one of the 10 diagnostic fields (Table I). Method II identified patients through an algorithm based on the definition of anaphylaxis proposed at the 2005 meeting of the NIAID/FAAN.¹ Analyses of cases ascertained through the algorithm (ie, Method II) excluded all cases that were first ascertained through Method I. This algorithm identifies patients with features of the anaphylactic syndrome sufficient to make a diagnosis of anaphylaxis. A case of anaphylaxis was identified through Method II if respiratory compromise or skin-mucosal involvement was found in conjunction with shock caused by anesthesia, respiratory compromise or reduced blood pressure was found in conjunction with skin-mucosal involvement, or a combination of gastrointestinal symptoms, respiratory compromise, reduced blood pressure, or skin mucosal involvement was found in conjunction with a potential allergen (including venom, drugs, or a biological substance). These were identified through ICD-9-CM codes found within the 10 diagnostic fields and 3 external cause-of-injury code fields (Table I).

Exclusion criteria

A total of 3,024 records of anaphylaxis were identified by using Method I ($n = 1,283$) and Method II ($n = 1,741$). Analysis was restricted to records for Florida residents. Two hundred fifty-four nonresident records were excluded, which yielded 2,770 Florida cases. Subjects were also excluded from the analysis if the envenomation, as determined through ICD-9-CM code 989.5, was from an animal or plant whose venom is likely to produce signs and symptoms that result from direct venom toxicity rather than anaphylaxis (snakes/lizards [E905.0], venomous spiders [E905.1], and marine animals/plants [E905.6]). Nineteen such cases were identified: 2 were envenomations from snakes/lizards, 8 were envenomations from venomous spiders, and 10 were envenomations from marine animals/plants. There were 2,751 records used in the analysis that met either definition of anaphylaxis in Florida residents.

Anaphylactic triggers

After a case of anaphylaxis was identified by using either Method I or II, the causes of anaphylaxis were examined. Each trigger was identified by searching for a related ICD-9-CM code. A patient was identified as having a food-related

reaction if they experienced dermatitis caused by food (693.1), anaphylaxis caused by a food allergy (995.60-995.69), or an adverse food reaction that was not classified elsewhere (995.7). Because of the relationship between the 2 methods of case ascertainment, subjects with an ICD-9-CM code of 995.60 to 995.69 (anaphylaxis caused by a food allergy) were automatically identified by using Method I. It was not possible to identify the specific food trigger for the few subjects identified with food-induced anaphylaxis by using the algorithm (Method II). Medication-induced anaphylaxis was identified by using the algorithm when a patient record indicated dermatitis caused by a medication (693.0) or an adverse reaction to a drug (995.2 and 995.4) or the patient had taken an antibiotic/anti-infective (E930-E930.9 and E931-E931.9). Patients with Hymenoptera venom-induced anaphylaxis presented with a sting or stings from a hornet, wasp, or bee (E905.3) or a sting from other venomous arthropods (E905.5) or included patients whose records indicated the toxic effect of venom (989.5). The ICD-9-CM code 989.5 is often used to categorize patients with Hymenoptera insect stings.¹⁰

Demographic factors

Demographic factors examined included the age of the patient at the time of an ED visit, race, ethnicity, and sex. The principal payer was used as a proxy for the patient's socioeconomic status and was combined into 3 categories: commercial insurance, governmental insurance, and no insurance. Commercial insurance carriers included non-Medicaid health maintenance organizations and preferred provider organizations. Governmental insurance carriers included Medicare, Medicaid, the Department of Veteran Affairs, and government-sponsored health care plans, such as prison and health department clinics. Patients whose principal payer was through charity, self-pay, or other were categorized as having no insurance. Employees of the federal government have employer-provided commercial health insurance.

Clinical factors

The clinical factors used in the analysis were hypertension, heart disease, asthma, shortness of breath, tachypnea, wheezing, and chronic obstructive pulmonary disease (COPD). Patients with these factors were identified by the presence of the related ICD-9-CM code. Patients with hypertension or heart disease had codes for hypertensive disease (401-402.9 and 404-405.99), coronary atherosclerosis (414.00-414.05), or congestive heart failure (428.0-428.9). Asthmatic patients were identified by using the ICD-9-CM codes 493 through 493.92. COPD was defined by chronic airway obstruction (496) and obstructive chronic bronchitis with acute exacerbation (491.21). Shortness of breath, tachypnea, and wheezing were identified by using their specific ICD-9-CM codes: 786.05, 786.06, and 786.07, respectively. Codes used to identify epinephrine use were the ICD-9-CM codes E941.2 and E933.0 and Current Procedural Terminology codes J0170, J1200, J2920, and J2930.

Calculation of ED visit rates

Age- and sex-specific rates for patients treated in Florida EDs were calculated by dividing the appropriate number of anaphylaxis cases by the sum of the stratum-specific Florida population estimate for 2005 and 2006. The χ^2 test for linear trend in proportions was calculated for both the male and female rates by using SAS software (SAS Institute, Inc, Cary, NC). Age-adjusted rates stratified by sex were calculated by using the 2000 US standard population.¹¹ In addition, the proportion of anaphylaxis cases by month was compared with the proportion of monthly ED visits by using the χ^2 goodness-of-fit test.¹²

Comparison of methods

Descriptive statistics and ED visit rates were presented stratified by the method of anaphylaxis case ascertainment. This separation of cases allowed for the comparison of patients' demographic and clinical risk factors by using the 2 case-ascertainment strategies. The risk factors were then compared by using the Pearson χ^2 test, except for total patient charges and age, which were both defined as continuous. The medians and means of these variables were compared by using a z test or the Mann-Whitney-Wilcoxon test. Demographic

TABLE I. ICD-9-CM criteria for case-ascertainment methods

Method I: Codes for anaphylactic shock	● Anaphylactic shock caused by food (995.60-995.69) ● Other anaphylactic shock (995.0)
Method II: ICD-9-CM algorithm	● Skin-mucosal tissue involvement was found in conjunction with shock caused by anesthesia (995.4) ● Respiratory compromise was found in conjunction with shock caused by anesthesia (995.4) or angioneurotic edema (995.1) ● Reduced blood pressure was found in conjunction with skin-mucosal involvement, angioneurotic edema (995.1), the toxic effect of venom (989.5), or an Ecode indicating the cause of poisoning was a venomous animal/plant (E905, E905.3, E905.5, E905.8, E905.9) ● Reduced blood pressure and gastrointestinal symptoms were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3) ● Reduced blood pressure and skin-mucosal tissue involvement were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3) ● Respiratory compromise and reduced blood pressure were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3) ● Respiratory compromise and gastrointestinal symptoms were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2); an unspecified allergic reaction (995.3); skin-mucosal involvement; the toxic effect of venom (989.5); or an Ecode indicating the cause of poisoning was a venomous animal/plant (E905, E905.3, E905.5, E905.8, E905.9) ● Respiratory compromise and skin-mucosal tissue involvement were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2); an unspecified allergic reaction (995.3); the toxic effect of venom (989.5); or an Ecode indicating the cause of poisoning was a venomous animal/plant (E905, E905.3, E905.5, E905.8, E905.9) ● Gastrointestinal symptoms and skin-mucosal tissue involvement were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2); an unspecified allergic reaction (995.3); the toxic effect of venom (989.5); or an Ecode indicating the cause of poisoning was a venomous animal/plant (E905, E905.3, E905.5, E905.8, E905.9)
Definition of symptom categories	● Respiratory compromise: acute respiratory failure (518.81), acute respiratory distress (518.82), dyspnea/respiratory distress (786, 786.00-786.09), stridor (786.1), extrinsic asthma (493.0), or unspecified asthma (493.9) ● Reduced blood pressure: hypotension (458, 458.0, 458.2, 458.8, 458.9) or syncope/collapse (780.2) ● Gastrointestinal symptoms: allergic gastroenteritis/colitis (558.3), nausea/vomiting (787.0), nausea with vomiting (787.01), vomiting alone (787.03), or abdominal pain (789.0) ● Skin-mucosal involvement: conjunctival edema (372.73), edema of eyelid (374.82), edema of larynx (478.6), edema of pharynx or nasopharynx (478.25), flushing (782.62), urticaria (708), allergic urticaria (708.0), idiopathic urticaria (708.1), urticaria caused by cold and heat (708.2), dermatographic urticaria (708.3), vibratory urticaria (708.4), cholinergic urticaria (708.5), other specified urticaria (708.8), unspecified urticaria (708.9), pruritus and related conditions (698), pruritus of genital organs (698.1), other specified pruritic conditions (698.8), unspecified pruritic disorder (698.9)

Ecode, External cause-of-injury code.

factors of age (defined as categorical), sex, race, and ethnicity were also compared with the distribution of these factors in the state population by using the χ^2 goodness-of-fit test.¹²

RESULTS

ED cases ascertained by using anaphylaxis-specific ICD-9-CM codes (Method I)

A total of 1,149 ED anaphylaxis cases were directly identified by using only ICD-9-CM codes specific to this condition. The age-adjusted rate was 3.3 cases per 100,000 Floridians per year (95% CI, 1.4-5.2). Eighty-seven percent ($n = 1,000$) of cases included a primary diagnosis of anaphylactic shock. Anaphylactic shock was listed as a secondary diagnosis for the other cases. The demographic composition of subjects identified with anaphylaxis by using Method I (Table II) was slightly different from the general Florida ED population. However, the differences in proportions were less than 5% (see Table E1 in this article's Online Repository at www.jacionline.org). The mean age for

subjects given a diagnosis of anaphylaxis in the ED was 35.1 years, which is lower than the mean age for the state population (39.8 years). The difference between the mean age of the anaphylactic patients (35.1 years) and the mean age (33.8 years) of all ED patients approached statistical significance, with a P value of .05. Additionally, the distribution of cases by age group differed by sex, with a P value of .001 (see Fig E1 in this article's Online Repository at www.jacionline.org).

Approximately half ($n = 596$) of the subjects identified with anaphylaxis by using Method I had accompanying diagnostic codes indicating the anaphylaxis trigger. The most common trigger was food related ($n = 451$) followed by medication ($n = 109$) and venomous insect stings ($n = 36$). Among the subjects with food-induced anaphylaxis, 408 had a primary diagnosis of anaphylactic shock caused by food (ICD-9-CM codes 995.60-69). The most frequently ($n = 154$) specified category for food-induced cases was anaphylaxis caused by an unknown food (995.69) or a food not specified (995.60). The most commonly specified foods were peanuts ($n = 89$) and fish ($n = 79$). Almost

TABLE II. Demographic and clinical characteristics of patients treated for anaphylactic shock in Florida EDs for the years 2005 and 2006 (n = 2751)*

	Type of case definition				P value
	Method I (n = 1149)		Method II, algorithm (n = 1602)		
	No.	Percentage	No.	Percentage	
Demographic variables					
Total charges†	\$1307 (\$1422)		\$1257 (\$1484)		.17
Age (y)‡	35 (22.0)		41 (20.7)		<.0001
Male sex	507	44	666	42	.08
Female sex	642	56	936	58	
White	914	81	1276	80	.61
Black	176	16	260	16	
Other	44	4	52	3	
Hispanic	175	15	216	14	.18
Non-Hispanic	959	85	1372	86	
Commercial insurance	603	52	766	48	.04§
Government insurance	313	27	497	31	
No insurance	233	60	339	21	
Clinical variables					
Asthma	91	8	129	8	.90
Heart disease	134	12	310	19	<.0001
Shortness of breath (786.05)	81	7	638	40	<.0001
Tachypnea (786.06)	2	0	5	0	.71
Wheezing (786.07)	26	2	173	11	<.0001
COPD (491.2, 496)	10	1	22	1	.23
Venom (Ecode)	36	3	255	16	<.0001
Food related	451	39	46	3	<.0001
Medical related	109	9	119	7	.05
Epinephrine administration	111	10	180	11	.19

Ecode, External cause-of-injury code.

*Fourteen subjects in Method II and 15 subjects in Method I did not provide race/ethnicity.

†Reported as median (interquartile range) with the Mann-Whitney-Wilcoxon test.

‡Reported as mean (standard deviation) with the z test. Note: When cases with food-related triggers are removed, there is still a difference between mean ages ($P = .01$).§There is a difference between commercial and governmental insurance ($P = .01$).

all (n = 106) cases of medication-induced anaphylaxis were due to antibiotics or other anti-infectives (Table III). When specified, the 3 most commonly identified drug groupings were penicillin (n = 37), other or unspecified antibiotics (n = 31), and cephalosporins (n = 14). Sixty-seven percent (n = 24) of the cases given a diagnosis of anaphylaxis triggered by a venomous insect sting were due to a hornet, wasp, or bee sting, and 28% (n = 10) of patients were bitten by a venomous arthropod (Table III). There were 700 cases identified by using Method I with an ICD-9-CM code of 995.0 (other anaphylactic shock). A food trigger was identified in 2, a venom trigger in 36, and a medication trigger in 109.

Anaphylaxis cases identified by using Method I were seen in the ED less frequently during the first quarter (January, February, and March) of the year than at other times (see Fig E2 in this article's Online Repository at www.jacionline.org). The highest crude rate of anaphylaxis-induced ED visits was found in December (12.4 per 100,000 ED visits). However, there was no statistically significant difference between anaphylaxis-induced monthly ED visits and the proportion of all ED visits made by Floridians. Among subjects whose anaphylactic trigger was identified, only those with venom-induced anaphylaxis had a significantly different proportion of monthly visits compared with the proportion of all ED visits ($P < .0001$), with 22% of cases occurring in September.

ED anaphylaxis cases ascertained by using the anaphylaxis algorithm (Method II)

The anaphylaxis algorithm identified an additional 1,602 ED cases among Floridians for 2005 and 2006, which produced an age-adjusted rate of 4.4 cases per 100,000 Floridians (95% CI, 2.2-6.6). The number of subjects identified in each algorithm criteria category is shown in Table E2 (available in this article's Online Repository at www.jacionline.org). The demographic profile of subjects given diagnoses of anaphylaxis identified by using Method II (algorithm, Table II) was slightly different from that of the general ED Florida population (see Table E1). Again, the differences in proportions were less than 10%. The mean age was 41.2 years for subjects ascertained by using Method II, which was slightly higher than the mean age for the state population (39.8 years) and significantly higher than the mean age (33.8 years) of the overall ED population ($P < .0001$, see Table E1). Additionally, the distribution of cases by age group differed by sex ($P = .01$, see Fig E1).

Information on anaphylactic triggers, as assessed by using accompanying diagnostic codes, were found in the ED record less often for those patients identified through Method II (n = 420 [26%]) than for those patients identified through Method I (n = 601 [41%]). The most common trigger for patients identified by using the algorithm was venomous insect stings (n = 255) followed by medication (n = 119) and food (n = 46). Half

TABLE III. Patients treated in Florida EDs for anaphylactic shock caused by antibiotics or anti-infectives, food, and Hymenoptera insect venoms for the years 2005 and 2006

Description of diagnosis	Type of case definition			
	Method I		Method II, algorithm	
	No.	Percentage	No.	Percentage
Antibiotics or anti-infectives				
Penicillins	37	35	9	18
Erythromycin and other macrolides	4	4	4	8
Tetracycline group	0	0	2	4
Cephalosporin group	14	13	6	12
Other/unspecified antibiotics*	31	29	15	29
Sulfonamides	8	8	6	12
Quinoline and hydroxyquinoline derivatives	4	4	4	8
Other antiprotozoal drugs	0	0	2	4
Other and unspecified anti-infectives	8	8	3	6
Total	106	100	51	100
Hymenoptera insect venoms				
Hornets, wasps, or bees	24	67	130	51
Other venomous arthropods	10	28	104	41
Toxic effect of venom	2	6	21	8
Total	36	100	255	100
Food				
Dermatitis caused by food	2	0	22	48
Anaphylaxis caused by a food allergy	449	100	0	0
Adverse food reaction not classified elsewhere	0	0	24	52
Total	451	100	46	100

*Other antibiotics = E930, E930.8, and E930.9.

($n = 130$) of the subjects with venom-induced anaphylaxis were stung by a hornet, wasp, or bee (Table III). An additional 40% ($n = 104$) of cases were due to a bite by a venomous arthropod. By using Method II, among anaphylaxis cases caused by medication, less than half ($n = 51$) were due to antibiotics or other anti-infectives (Table III). The most commonly mentioned drug groupings were other or unspecified antibiotics ($n = 15$), penicillins ($n = 9$), cephalosporins ($n = 6$), and sulfonamides ($n = 6$). In the overall group identified by using the algorithm, 22 cases were treated for dermatitis caused by food, and 24 cases were treated for other food reactions. Thus 46 cases of food-related anaphylaxis were identified with the algorithm. This is in contrast to anaphylaxis cases ascertained through Method I, where 451 food-related cases were identified but only 2 cases listed the ICD-9-CM code for dermatitis caused by food (693.0) and none listed other food reactions (995.7). The specific food that caused the anaphylactic reaction for those cases ascertained by using Method II (algorithm) could not be determined from the available diagnostic codes. Patients who had food-induced anaphylaxis for which the food had a specific ICD-9-CM code are automatically identified by using Method I.

The highest crude rate of anaphylaxis cases identified through the algorithm occurred in August (18.8 per 100,000 ED visits) and September (18.7 per 100,000 ED visits, see Fig E2). The difference between the distribution of anaphylaxis cases by month and the distribution of all monthly ED visits made by Floridians

was statistically significant ($P < .0001$). The majority of this difference can be attributed to venom-induced anaphylaxis cases. Without these cases, the difference in distribution is not significant ($P = .06$). Venom-induced anaphylaxis cases occur most frequently in August (15%), September (15%), and October (14%). It is important to note that the distribution of anaphylaxis cases without a known trigger identified through Method II ($n = 1,182$) was not statistically different from the distribution of all monthly ED visits ($P = .05$).

Comparison of ascertainment method

A total of 2,751 ED cases of anaphylaxis were identified by using either case-ascertainment method; 42% were identified through Method I, and 58% were identified by using the algorithm (ie, Method II). There were 26 cases that could have been identified by using either method. However, because of study criteria, these cases were classified as Method I. The demographic information for anaphylaxis cases ascertained by using the 2 methods was very similar (Table II). The majority of all anaphylaxis cases involved white, non-Hispanic female subjects. The main difference was in age at the time of treatment. Those subjects identified by using anaphylaxis-specific ICD-9-CM codes were significantly younger (35 vs 41 years) than those subjects identified by using the algorithm ($P < .0001$). Twenty-two percent of cases ascertained by using ICD-9-CM codes specific to anaphylaxis involved subjects 14 years or younger compared with only 10% of cases ascertained by using the algorithm (see Fig E1).

Patients identified by using anaphylaxis-specific ICD-9-CM codes were also more likely to have commercial insurance than governmental insurance compared with subjects given diagnoses by using the algorithm ($P = .01$). Of note, there was no difference between the 2 groups for the median patient cost of treatment before any discounts ($P = .17$).

The same proportion (8%) of subjects in each case-ascertainment group had a diagnosis indicating the presence of asthma. However, a larger proportion of subjects with anaphylaxis ascertained by using the algorithm had hypertension or heart disease compared with those with anaphylaxis-specific ICD-9-CM codes ($P < .0001$). Forty percent of subjects identified with anaphylaxis by using the algorithm had additional diagnostic codes for shortness of breath compared with only 7% of subjects identified by ICD-9-CM codes for anaphylaxis ($P < .0001$). Wheezing was also seen more often in patients identified through Method II compared with those patients identified through Method I ($P < .0001$). The other respiratory conditions, COPD and tachypnea, were rarely seen in either group.

A greater proportion of anaphylaxis cases identified by using the algorithm were related to insect stings than were cases identified by using only anaphylaxis ICD-9-CM codes ($P < .0001$). In contrast, a greater proportion of food-induced anaphylactic shock cases were found among subjects identified by anaphylaxis-specific ICD-9-CM codes compared with the cases ascertained by using the algorithm ($P < .0001$). The differences in the proportion of medication-related anaphylaxis cases identified through Method I compared with the proportion identified through Method II approached statistical significance ($P = .05$).

An epinephrine treatment code was used in 111 cases identified by using Method I (10%) and 180 cases by using Method II (11%, Table II). These frequencies were not statistically different ($P = .19$).

The distribution of monthly anaphylaxis-induced visits to Florida EDs differs depending on the case-ascertainment method ($P < .0001$). The rate of ED visits for cases identified through Method I decreased slightly between January and April, whereas the rate for cases identified through Method II increased during the same time period. Toward the end of the year, the crude rate of ED visits increased for subjects identified through Method I and was relatively stable for patients identified through Method II (see Fig E2).

DISCUSSION

The epidemiology of anaphylaxis is not very well understood. This is exemplified by the fact that published estimates on the burden of disease within the population vary widely.⁸ This problem might be due, in large part, to underdiagnosis and misdiagnosis of this multiple-system multiorgan syndrome. Underdiagnosis during clinical care can lead to the undertreatment of anaphylaxis.⁴ The lack of availability of ICD-9-CM codes for anaphylaxis diagnosis without shock contributes to this underdiagnosis.¹³ The need for a better definition and method of case ascertainment in the epidemiologic study of anaphylaxis is important. In 2006, an anaphylaxis definition and diagnostic criteria were published based on the results of the 2005 NIAID/FAAN symposium.¹ This definition outlined a method for identifying and diagnosing patients with anaphylaxis. The use of this definition, as in the algorithm used by Bohlke et al,¹⁴ lends itself to extracting cases during medical record review and capturing acuteness of onset of anaphylactic signs and symptoms. However, it cannot be used in epidemiologic studies, which depend on ICD-9-CM–based administrative data. We have modified the NIAID/FAAN anaphylaxis definition so that it can be used with ICD-9-CM–based administrative datasets to capture previously unidentified cases of anaphylaxis. The algorithm presented in our work includes all the possible combinations of signs and symptoms necessary to make a diagnosis of anaphylaxis that can be included in ICD-9-CM coding. The algorithm case-ascertainment method (Method II) was compared with the traditional method of extracting cases by using ICD-9-CM codes specific to anaphylactic shock (Method I).

The demographic information (sex, race, and ethnicity) among the 2 groups was not statistically different. The median medical charges per visit were similar, indicating comparable treatments between groups. Furthermore, prior studies examining the differences in the frequency of anaphylaxis during the progression of the seasons of the year show an increase in cases during the third quarter (July, August, and September).^{2,5,15,16} These results were seen in both case-ascertainment groups, although the increase during the third quarter was more pronounced in patients identified through Method II, further supporting the accuracy of this case-ascertainment method. Although the proportions of patients with medication-induced anaphylaxis identified using Method I versus Method II approached statistical significance, with a P value of .05, the proportions only differed slightly, with 9% and 7% respectively.

There were some demographic differences found between the 2 populations ascertained by using Methods I and II. The mean age (41 years) of patients identified by using Method II (algorithm) is significantly older than the mean age (35 years) seen in patients identified by using Method I, even when all food-triggered anaphylaxis cases are removed from the analysis. However, the

difference in mean age between the groups is decreased by the removal of all food-triggered anaphylaxis cases (Table II). Therefore the true mean age of patients treated in the ED with anaphylaxis might be somewhat older than previously reported.^{3,17,18}

The algorithm (Method II) identified proportionally more cases of venom-induced anaphylaxis than Method I. This indicates that the algorithm functions as expected. In addition, this finding was surprising because clinicians and the public are generally aware that Hymenoptera stings can cause anaphylaxis. It would be expected that this awareness would result in the use of the specific anaphylactic diagnostic codes indicating a Hymenoptera trigger. Our results suggest that the frequency of Hymenoptera sting-induced anaphylaxis might be greater than previously appreciated. Previously reported prevalence estimates are based on expert history or questionnaires in community based studies and not on ICD-9-CM code based case findings.¹⁹⁻²¹

ICD-9-CM codes 995.60 through 995.69 amply identify food-induced anaphylaxis. The algorithm (Method II) identified very few additional food-induced anaphylaxis cases. This would suggest that data from our study can be compared with published estimates of the overall frequency of food-induced anaphylaxis cases previously identified by using ICD-9-CM codes. Nevertheless, there might be an underuse of ICD-9-CM codes specific to food reactions, as indicated in a 2006 study.¹⁰ Clark et al¹⁰ identified only half of their cohort of patients with food allergies through specific food-related ICD-9-CM codes. The rest of the patients were identified through a medical records review. Because a medical records review was not conducted in our study, we cannot estimate the percentage of food-induced anaphylaxis cases that might still be unidentified.

ICD coding in EDs appears to be more likely to include a code for food anaphylaxis, whereas Hymenoptera sting reactions are more likely to be coded “symptomatically” without the use of an anaphylaxis code. Another difference between Methods I and II could be that when the case is coded with an anaphylaxis code (Method I), it is less likely that other descriptive codes, such as codes for the clinical variables of shortness of breath and wheezing, would have been used because the diagnosis was already clear. When the case is identified by the algorithm (Method II), these clinically important respiratory signs and symptoms are more likely to be documented.

A strength of this study includes the very large number of patients included and the large number of institutions from which they are drawn. This allows for robust statistical conclusions and minimizes coding, treatment biases, or both specific to a single institution. Limitations of this study are first that it was not possible to confirm the coding information by means of manual case abstraction or the presence of an anaphylaxis expert at the patients’ bedsides. The report by Clark et al¹⁰ discussing the underuse of ICD-9-CM codes to identify food reactions demonstrates the limitations of ICD-9-CM codes when compared with medical record review. That notwithstanding, the frequency of use of epinephrine in the group identified by using Method I (ICD-9-CM anaphylaxis codes) and the group identified by using Method II (algorithm) was not statistically different (Table II). This suggests that both groups contained similar proportions of subjects who were treated acutely for anaphylaxis. The frequency of epinephrine use found in this study is lower than previously reported.²² This might reflect the administration of epinephrine in some patients before their arrival in the ED. It also might result from the inadequate use of ICD-9-CM and Current Procedural

Terminology codes for epinephrine use. There is the possibility that there are scenarios that could be mistaken for anaphylaxis by the algorithm. However, a careful review of the algorithm components only revealed 2 possible cases (of 1,602) in which there were clinical scenarios that could have been mistakenly identified as anaphylaxis. These 2 subjects were identified by using Method II on the basis of having had stridor and cutaneous angioedema. Finally, it is not possible to determine the positive and negative predictive values for either method because an anaphylaxis expert was not present to make critical real-time observations. This study has not elucidated the epidemiology of anaphylaxis in the population as a whole because many patients with anaphylaxis might not present to an ED.

This study is the first to develop and validate a diagnostic algorithm for anaphylaxis that identifies cases based on ICD-9-CM codes for anaphylactic signs and symptoms. We have demonstrated that 58% of anaphylaxis cases remain undiagnosed if only the ICD-9-CM codes for anaphylaxis are used to identify cases.

Clinical implications: The ICD-9-CM–based diagnostic algorithm when used together with the anaphylaxis ICD-9-CM codes allows for a more accurate estimate of the incidence of anaphylaxis by capturing previously unidentified cases, especially venom-induced cases.

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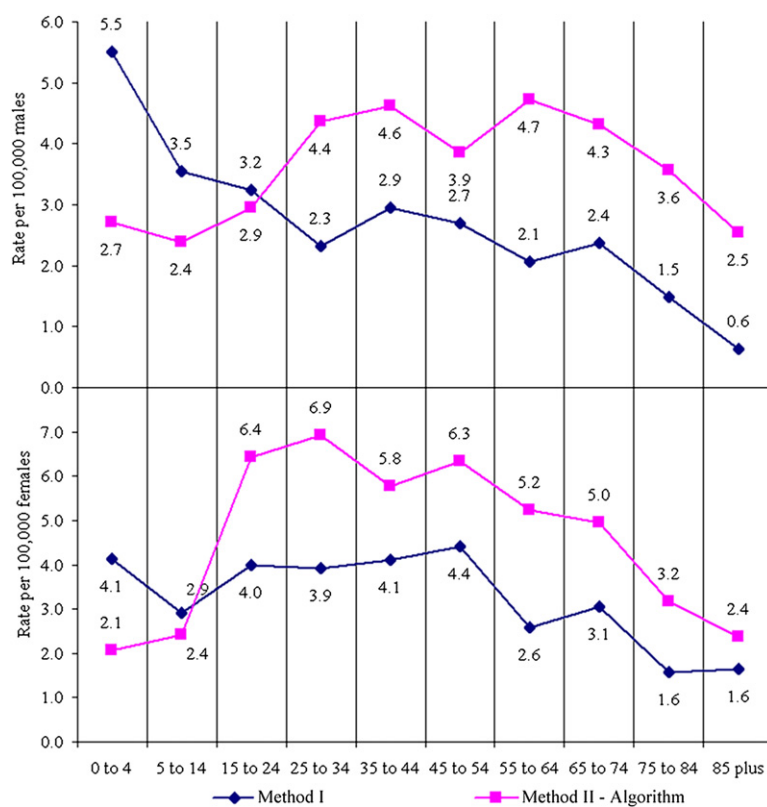


FIG E1. Age-specific rates for male ($n = 1241$) and female ($n = 1578$) subjects treated for anaphylactic shock in Florida EDs for the years 2004 and 2005. The distribution of anaphylaxis cases stratified by sex are different for both case-ascertainment methods (Method I, $P = .001$; Method II, $P = .01$). Rates were calculated by using the age- and sex-specific Florida population for the years reported.

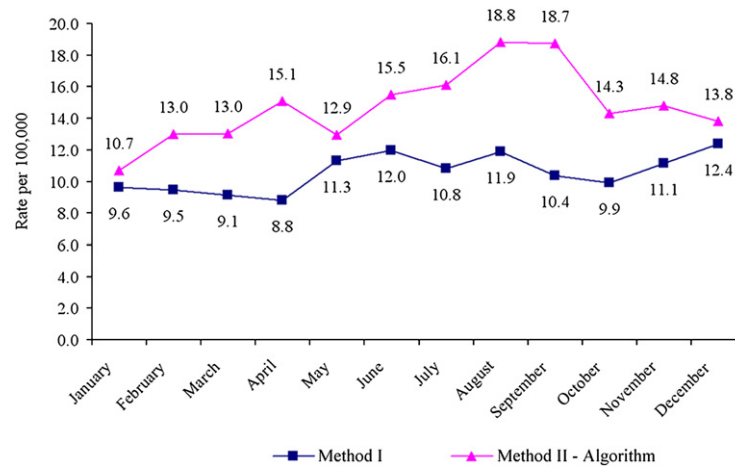


FIG E2. Crude monthly rates for patients treated in Florida EDs for anaphylactic shock for the years 2004 and 2005. Denominators for rates were the total number of monthly visits to Florida EDs for all conditions.

TABLE E1. Demographic characteristics of patients treated for anaphylactic shock identified by ICD-9-CM specific codes in Florida EDs compared with all ED visits for the years 2005 and 2006

	All ED visits (n = 10,899,111)		ICD-9-CM codes (n = 1149)			Algorithm (n = 1602)		
	Count	Mean	Count	Mean	<i>P</i> value*	Count	Mean	<i>P</i> value*
Mean age	10,899,148	33.8	1149	35.1	.05	1602	41.2	<.0001
	Count	Proportion (%)	Count	Proportion (%)	<i>P</i> value*	Count	Proportion (%)	<i>P</i> value*
Male sex	4,940,593	45.3	507	44.1	.41	666	41.6	.003
Female sex	5,958,518	54.7	642	55.9		936	58.4	
White	8,086,029	74.7	914	80.6	<.0001	1276	80.4	<.0001
Black	2,473,444	22.8	176	15.5		260	16.4	
Other	268,843	2.5	44	3.9		52	3.3	
Hispanic	1,737,784	16.1	175	15.4	.57	216	13.6	.008
Non-Hispanic	9,090,532	84.0	959	84.6		1372	86.4	
Commercial insurance	3,815,452	35.0	603	52.5	<.0001	766	47.8	<.0001
Government insurance	4,194,097	38.5	313	27.2		497	31.0	
No insurance	2,889,674	26.5	233	20.3		339	21.2	

*Comparison group is all ED visits.

TABLE E2. Frequency of occurrence for each algorithm (Method II) criterion used to identify anaphylaxis*

Skin-mucosal tissue involvement was found in conjunction with shock caused by anesthesia (995.4)	0
Respiratory compromise was found in conjunction with shock caused by anesthesia (995.4)	0
Respiratory compromise was found in conjunction with angioneurotic edema (995.1)	297
Reduced blood pressure was found in conjunction with angioneurotic edema (995.1)	14
Reduced blood pressure was found in conjunction with skin-mucosal involvement	298
Reduced blood pressure was found in conjunction with the toxic effect of venom (989.5)	3
Reduced blood pressure was found in conjunction with an Ecode indicating the cause of poisoning was a venomous animal/plant (E905, E905.3, E905.5, E905.8, E905.9)	110
Reduced blood pressure and gastrointestinal symptoms were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)	11
Reduced blood pressure and skin-mucosal tissue involvement were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)	0
Respiratory compromise and reduced blood pressure were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)	16
Respiratory compromise and gastrointestinal symptoms were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)	55
Respiratory compromise and gastrointestinal symptoms were found in conjunction with skin-mucosal involvement	73
Respiratory compromise and gastrointestinal symptoms were found in conjunction with the toxic effect of venom (989.5)	0
Respiratory compromise and gastrointestinal symptoms were found in conjunction with an Ecode indicating the cause of poisoning was a venomous animal/plant (E905, E905.3, E905.5, E905.8, E905.9)	10
Respiratory compromise and skin-mucosal tissue involvement were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)	534
Respiratory compromise and skin-mucosal tissue involvement were found in conjunction with the toxic effect of venom (989.5)	1
Respiratory compromise and skin-mucosal tissue involvement were found in conjunction with an Ecode indicating the cause of poisoning was a venomous animal/plant (E905, E905.3, E905.5, E905.8, E905.9)	114
Gastrointestinal symptoms and skin-mucosal tissue involvement were found in conjunction with an unspecified adverse effect caused by the correct administration of a drug, medicinal, and biologic substance (995.2) or an unspecified allergic reaction (995.3)	77
Gastrointestinal symptoms and skin-mucosal tissue involvement were found in conjunction with the toxic effect of venom (989.5)	2
Gastrointestinal symptoms and skin-mucosal tissue involvement were found in conjunction with an Ecode indicating the cause of poisoning was a venomous animal/plant (E905, E905.3, E905.5, E905.8, E905.9)	13

Ecode, External cause-of-injury code.

*Note anaphylaxis cases may have been identified through more than one criterion and therefore do not add to the total number of cases identified using method II (n = 1602).