immunohistochemical stains for CMV, adenovirus, HSV1, and HSV2 and molecular analyses for EBV, CMV, and other herpes viruses were negative. Similar liver pathology was previously observed in a patient with complete ADA deficiency that improved after treatment with PEG-ADA.[5] In contrast, administration of PEG-ADA in this patient had no effect on alanine aminotransferase levels, which continued to increase over a period of 6 months. Repeated liver biopsy showed some deterioration. Prednisone was therefore administered at a dose of 1 g/kg/d, resulting in a sustained improvement with complete resolution in 3 months. Treatment was discontinued after 3 months, and liver enzyme levels remained normal for more than 18 months. This response to treatment together with the panel of autoantibodies detected in the serum suggested that the pathology in the liver of our patient was predominantly caused by autoimmune inflammation rather than a direct toxic effect of adenosine metabolites.

We report here lung and liver changes that caused severe morbidity in a patient with partial ADA deficiency. Because partial ADA deficiency might not be detected early, it is important to recognize these clinical and pathologic features, which could be the presenting manifestations of ADA deficiency and can be reversed with PEG-ADA or immunosuppression.

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Higher incidence of pediatric anaphylaxis in northern areas of the United States

To the Editor:

Anaphylaxis is a severe allergic reaction that has a rapid course and can result in death.[1] Similar to other allergic diseases, the incidence of anaphylaxis has increased over the past few decades.[2-4] Recent estimates suggest a lifetime prevalence of 0.05% to 2.0%,[5] with food allergy being the most common cause.[2,6] One approach was to indirectly estimate the incidence of anaphylaxis by analyzing medication-dispensing data for epinephrine.[7] Camargo et al[8] used this method to demonstrate a north-south gradient of EpiPen (Dey L.P., Napa, Calif) prescriptions, with the highest rates found in northern states. Our study scrutinized the incidence of pediatric anaphylaxis with a specific focus on a north-south comparison. To do this, we analyzed a large national billing database of US pediatric hospitals for all patient encounters billed as anaphylaxis.

Data for this study were obtained from the Pediatric Health Information System, an administrative database that contains

TABLE I. Basic demographics of cases of anaphylaxis

	Northern United States (11 hospitals)		Southern United States (13 hospitals)		
	Absolute no.	Rate (per 1,000)	Absolute no.	Rate (per 1,000)	*P* value
Cases of anaphylaxis	3,704	0.88	2,753	0.63	<.001
Total patient visits	4,199,103		4,390,480		
Median age (y)	4.3		4.0		
Sex					
Male (cases)	2,018	0.90	1,453	0.61	<.001
Total visits	2,244,487*		2,372,381*		
Female (cases)	1,686	0.86	1,300	0.64	<.001
Total visits	1,954,393*		2,018,075*		
Race/ethnicity					
White/non-Hispanic (cases)	2,285	1.06	1,072	0.87	<.001
Total visits	2,159,145		1,230,543		
Black (cases)	671	0.62	924	0.56	.044
Total Visits	1,082,313		1,650,409		
Hispanic (cases)	207	0.52	475	0.44	.045
Total visits	401,791		1,089,432		
Asian (cases)	114	2.11	38	0.75	<.001
Total visits	53,943		50,809		
Native American (cases)	7	0.77	2	0.76	.991
Total visits	9,113		2,627		
Other (cases)	249	0.87	145	0.71	.054
Total visits	285,845		203,651		
Unknown (cases)	171	0.83	97	0.60	.010
Total visits	206,953		163,009		
Patient location					
Emergency department (cases)	2,640	0.78	1,725	0.49	<.001
Total visits	3,395,655		3,524,166		
Inpatient (cases)	1,064	1.32	1,028	1.19	.012
Total visits	803,448		866,314		

*There were 24 visits in the south and 223 visits in the north without a sex listed.

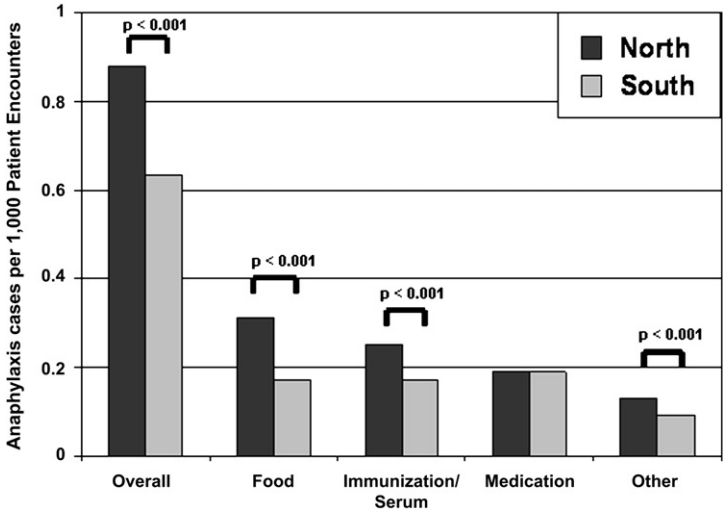

FIG 1. Rates of anaphylaxis by type of anaphylaxis. Each *bar* represents the identified cases of anaphylaxis per 1,000 patient encounters. *P* values represent the comparison of rates in the north with rates in the south (χ^2 test).

administrative and billing data from a group of tertiary care pediatric hospitals in the United States that are affiliated with the Child Health Corporation of America (Shawnee Mission, Kan), a business alliance of children's hospitals. We included all pediatric hospitals that contributed complete data from emergency department visits, inpatient admissions, and observation unit stays during a 5-year period from January 2003 to December 2007. There were 24 pediatric hospitals in 18 states across the United States that provided complete data during the entire study period. These hospitals were divided geographically at the line of 39°N latitude, extending roughly from Washington, DC, to Sacramento, California (see Fig E1 in this article's Online Repository at www.jacionline.org). As determined by the US Geological Society (www.usgs.gov), cities with a degree of latitude greater than 39°N were considered northern cities (n = 11), and cities south of 39°N were considered southern cities (n = 13).

We queried all cases in which the primary billing International Classification of Diseases, ninth revision, diagnosis code was specific for anaphylaxis. The diagnoses of anaphylaxis were classified by the type of anaphylaxis (see Table E1 in this article's Online Repository at www.jacionline.org). We did not include cases in which an anaphylaxis code was secondary or in which the code was not specific for anaphylaxis. Thus we did not include sting anaphylaxis because the code 989.5 ("toxic effect of venom") is not limited to or specific for anaphylaxis. We then used the Pediatric Health Information System database to calculate the total number of patient encounters at each of the hospitals during the study period. The number of anaphylaxis cases was divided by the total number of patient encounters to calculate an incidence (cases per 1,000 encounters). Incidences were calculated for each geographic region, each type of patient, and each coded type of anaphylaxis. Rates were compared, and rate ratios (RRs) with 95% CIs were calculated. Statistical significance was achieved with a 2-sided *P* value of less than .05, and analyses were performed with SPSS version 14 software (SPSS, Inc, Chicago, Ill).

We identified 6,457 cases of anaphylaxis among 8,589,583 patient encounters over the 5-year period. This is an incidence of 0.75 cases per 1,000 patient encounters. The median age of the subjects with anaphylaxis was 4.1 years, with 53.8% being male. Across the country, the incidence increased 50% during our study period, from 0.64 cases per 1,000 encounters in 2003 to 0.96 cases per 1,000 encounters in 2007 ($P < .001$).

The basic demographics of the cases of anaphylaxis are presented in Table I. Analysis of the northern hospital data revealed 3,704 cases of anaphylaxis among 4,199,103 patient encounters (rate of 0.88 cases per 1,000 encounters) compared with 2,753 cases of anaphylaxis among 4,390,480 patient encounters in the southern hospitals (rate of 0.63 cases per 1,000 encounters). Overall, this difference was statistically significant (RR, 1.41; 95% CI, 1.34–1.48; $P < .001$). Additionally, we compared degree of latitude with rate of anaphylaxis and found a statistically significant positive correlation ($r = 0.555$, $P = .005$). As seen in Table I, northern hospitals had statistically higher rates of anaphylaxis for all large subgroups of sex, race, and patient location.

Overall, the most common cause of anaphylaxis was food induced (n = 2,082 [32.2%]). This was followed by anaphylaxis caused by immunization or serum (n = 1,800 [27.9%]), medication (n = 1,627 [25.2%]), and unspecified or "other" causes (n = 946 [14.7%]). The comparison of northern hospitals with southern hospitals according to each type of anaphylaxis is seen in Fig 1. Anaphylaxis cases caused by food, immunization or serum, and "other" were all more common in the northern hospitals. In particular, the incidence of food anaphylaxis was almost double in the north compared with that in the south (0.31 vs 0.17; RR, 1.81; 95% CI, 1.66–1.98; $P < .001$). There was no statistical difference in the rates of medication-induced anaphylaxis between the north and south (0.19 vs 0.19; RR, 1.02; 95% CI, 0.92–1.12; $P = .73$).

This study is the first in the United States to evaluate the incidence of anaphylaxis on a national scale. Although we were unable to evaluate the true incidence in the general public, we were able to evaluate the rate of anaphylaxis cases per patient encounters at 24 hospitals in 18 states across the United States. We found a similar distribution of anaphylaxis as in previous studies,[2,6] with food-induced cases being the most common. The median age of our cases was low (approximately 4 years), with a male predominance (53.8%).

Although evaluated from a different perspective, our study also suggests higher rates of anaphylaxis in northern areas of the United States. Previous studies have used epinephrine distribution data, but instead, our study used primary billing diagnostic codes, thus eliminating prescription-writing bias. It has been suggested that this north-south gradient might be due to differences in vitamin D status. Although some studies have shown an inverse relationship between vitamin D status and risk of atopic illnesses,[9] more studies are needed in this area. Additionally, future studies are needed to evaluate for a north-south gradient for other atopic illnesses, such as asthma, allergic rhinitis, and eczema.

Of note, our study is representative of cases evaluated and treated at freestanding pediatric hospitals. As such, these hospitals are often referral centers providing tertiary care for all children in a certain city or state. It is difficult to assess how this might reflect incidence calculations for the general public. This might overestimate numbers if a large number of difficult anaphylaxis cases are referred to these hospitals. In contrast, it might underestimate incidence because anaphylaxis is an acute illness that is often treated immediately at local smaller hospitals. Also, our method of case identification by means of diagnostic billing codes might lead to errors in incidence calculation if anaphylaxis is inaccurately billed. However, both of these limitations occur in the north and south and should not affect the geographic comparison provided in our study.

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Associations between prenatal pesticide exposure and cough, wheeze, and IgE in early childhood

To the Editor:

Occupational and agricultural studies have reported positive associations between pesticide exposure and wheeze or asthma in adults.[1,2] Among elementary school children, exposures to herbicides, pesticides, and farm crops in the first year of life, determined retrospectively by questionnaire, were associated with asthma before age 5 years.[3] In a prospective birth cohort study in California, having a mother working in agriculture was associated with increased levels of T_H2 cytokines in children at age 2 years.[4] These associations have not been tested prospectively in children by using measured pesticide levels, nor in an urban cohort, in which residential pesticide use can be widespread.[5] We hypothesized that measured prenatal levels of pesticide would be associated with greater wheeze and IgE production by age 5 years among inner-city children living in Northern Manhattan and south Bronx.

The Columbia Center for Children's Environmental Health recruited nonsmoking African American and Dominican mothers during pregnancy as described.[6] The organophosphates chlorpyrifos and diazinon and the pyrethroids *cis*-permethrin and *trans*-permethrin were measured in personal air samples collected from monitors worn by women for 2 days during the last trimester of pregnancy. German cockroach allergen (Bla g 2) in house dust collected prenatally and serum IgE levels (antimouse, anticockroach, anti-*Dermatophagoides farinae*, anticat, antidog) at ages 2, 3, and 5 years were assessed by ELISA and ImmunoCAP, respectively, as described.[7] Prenatal questionnaires provided demographic information, characteristics of the home environment, including exposures to environmental tobacco smoke, and mother's health information. Parental questionnaires administered every 3 months from birth to age 2 years and every 6 months thereafter, and the International Study of Asthma and Allergy in Childhood question regarding asthma over the past year (age 5 years only), were used to derive respiratory symptom categories representing symptoms over the period of the previous 12 months at 2, 3, and 5 years. The mean $\pm$ SD ages of children at the administrations of 2-year, 3-year, and 5-year questionnaires were 2.0 $\pm$ 0.21, 3.1 $\pm$ 0.18, and 5.1 $\pm$ 0.67 years, respectively.

Pesticide and cockroach allergen were modeled as continuous variables after natural log-transformation. A child was considered to have wheezed (or coughed without cold) if there was any report on parental questionnaires of wheeze (or cough without cold) over the past year. A child was considered to be sensitized (dichotomous variable) if any of 5 specific IgEs measured $\geq$ 0.35 IU/mL.[7] The data were analyzed for cough, wheeze, and sensitization to any of 5 allergens using generalized estimating equations in multivariable models.

We found that pesticide use prenatally (personal home use methods and/or exterminator services) was reported by 87% of families. Eighty-two percent of the homes used pesticides any time postnatally through age 5 years. Table I exhibits the

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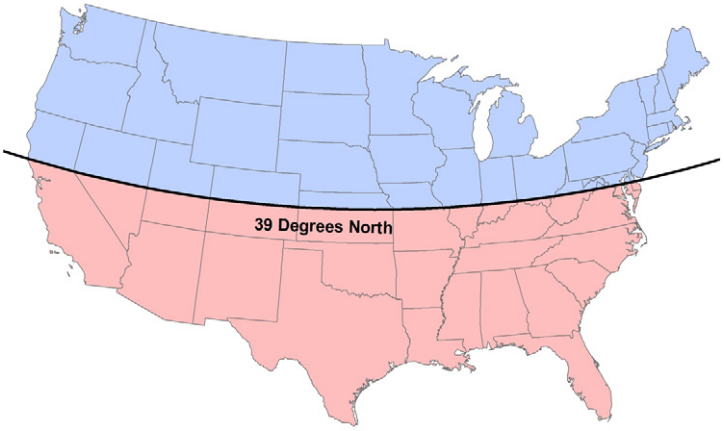

FIG E1. Map of the United States divided into north and south. This represents a map of the United States divided geographically at the line of 39°N latitude. We considered hospitals in cities above this line to be northern hospitals and those below the line to be southern hospitals.

TABLE E1. International Classification of Diseases, ninth revision, codes evaluated to determine cases of anaphylaxis

"Food" anaphylaxis
995.60 to 995.69: anaphylactic shock due to food (and specific foods)
"Immunization/serum" anaphylaxis
999.4: anaphylactic shock caused by immunization or serum
"Medication" anaphylaxis
977.9: anaphylactic shock caused by overdose or wrong substance given or taken
977.9: anaphylactic shock caused by specified drug
"Unspecified/other" anaphylaxis
995.0: anaphylactic shock or reaction NOS

The database was searched for cases having a primary International Classification of Diseases, ninth revision, code specific for anaphylaxis.