Ann Allergy Asthma Immunol 119 (2017) 339–348

Contents lists available at ScienceDirect

Multicenter prevalence of anaphylaxis in clinic-based oral food challenges

Kwei Akuete, MD, MPH [*,†]; Danielle Guffey, MS [‡]; Ryan B. Israelsen, MD [§]; John M. Broyles, MS, CRNP [§]; Lori Jo Higgins, LPN [||]; Todd D. Green, MD [§]; David R. Naimi, DO [||]; Andrew J. MacGinnitie, MD, PhD [¶]; Girish Vitalpur, MD [#]; Charles G. Minard, PhD [‡]; Carla M. Davis, MD [*,†]

[*] Immunology, Allergy, and Rheumatology Section, Texas Children's Hospital, Houston, Texas
[†] Department of Pediatrics, Baylor College of Medicine, Houston, Texas
[‡] Dan L. Duncan Institute for Clinical and Translational Research, Baylor College of Medicine, Houston, Texas
[§] Departments of Internal Medicine and Pediatrics, Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
[||] Northwest Asthma & Allergy Center, University of Washington School of Medicine, Seattle, Washington
[¶] Division of Immunology, Boston Children's Hospital Department of Pediatrics, Harvard Medical School, Boston, Massachusetts
[#] Section of Pediatric Pulmonology, Allergy, and Sleep Medicine Riley Hospital for Children at Indiana University Health, Indiana University School of Medicine, Indianapolis, Indiana

ARTICLE INFO

Article history:
Received for publication March 30, 2017.
Received in revised form July 20, 2017.
Accepted for publication July 24, 2017.

ABSTRACT

Background: Although previous single-center studies report the rate of anaphylaxis for oral food challenges (OFCs) as 9% to 11%, little is known regarding the epidemiology of clinical OFCs across multiple centers in the United States.

Objective: To examine the epidemiology, symptoms, and treatment of clinical low-risk OFCs in the nonresearch setting.

Methods: Data were obtained from 2008 to 2013 through a physician survey in 5 food allergy centers geographically distributed across the United States. Allergic reaction rates and the association of reaction rates with year, hospital, and demographics were determined using a linear mixed model. Meta-analysis was used to pool the proportion of reactions and anaphylaxis with inverse-variance weights using a random-effects model with exact confidence intervals (CIs).

Results: A total of 6,377 OFCs were performed, and the pooled estimate of anaphylaxis was 2% (95% CI, 1%-3%). The rate of allergic reactions was 14% (95% CI, 13%-16%) and was consistent during the study period ($P = .40$). Reaction rates ranged from 13% to 33%. Males reacted 16% more frequently than females (95% CI, 4%-37.5%; $P = .04$). Foods challenged in 2013 varied geographically, with peanut as the most challenged food in the Northeast, Midwest, and West and egg as the most challenged in the South.

Conclusion: As the largest national survey of allergic reactions of clinical open OFCs in a nonresearch setting in the United States, this study found that performing clinical nonresearch open low-risk OFCs results in few allergic reactions, with 86% of challenges resulting in no reactions and 98% without anaphylaxis.

Introduction

The double-blind, placebo-controlled food challenge OFC (DBPCFC) is currently recognized as the gold standard test for the presence or absence of food allergy.[1] The recommended evaluation of patients with food allergies includes detailed clinical history, serum specific IgE measurement, skin testing, and open oral food challenges (OFCs) for relevant food allergens. In adults, milk, shellfish, peanuts, and tree nuts have been reported as top allergens, whereas in children, these are allergens are cow's milk, nuts, and egg.[2] In clinical practice, DBPCFCs are time consuming and require more personnel compared with open OFCs. Therefore, the risk of reaction of OFCs predominantly performed in research-based clinical protocols has been assessed. However, there is a need to determine the safety of open OFCs because food allergies affect up to 6 million people,[3] and the health care cost for food allergies is $24 billion annually attributable to annual medical and out-of-pocket cost, lost labor productivity, and forgone caregiver labor market activities.[4]

It is paramount that physicians correctly identify true food allergies given the significant impairment in quality of life[5] and potential for nutritional deficiencies.[6] In addition, current studies have found that future food allergy therapies (oral immunotherapy,

Reprints: Carla M. Davis, MD, Immunology, Allergy, and Rheumatology Section, Texas Children's Hospital, 1102 Bates Ave, MC 330.01, Houston, TX 77030; E-mail: cmdavis@texaschildrens.org.

Disclosures: Authors have nothing to disclose.

http://dx.doi.org/10.1016/j.anai.2017.07.028

Table 1
Site-Specific Protocols

Protocol	Texas Children's Hospital	Boston Children's Hospital	Riley Hospital for Children	Children's Hospital of Pittsburgh	Northwest Asthma and Allergy Center
Protocol based on PRACTALL consensus report	Yes	No	No	No	Yes
Protocol based on OFC Work Group Report	Yes	No	Yes	Yes	No
Protocol based on practitioner-specific parameters	No	Yes	No	No	Yes
No. of doses in each food challenge	6–7	Low risk: 3 Higher risk: 6–7	7–8	6–8	4–6
Postchallenge observation period, min	120	30–60	60	60	60
Total time in the office for challenge, h	4–5	Low risk: 2 Higher risk: 3.5	4	3–4	4–6
Prick and prick testing used before day of challenge[a]	Yes	No	Yes	No	Yes

Abbreviations: OFC, oral food challenge; PRACTALL, PRACTALL Consensus Report.
[a]This was performed primarily for fruit and vegetable oral food challenges.

sublingual immunotherapy, and epicutaneous immunotherapy) are on the horizon.[7–12] If these therapies become standard of care, potentially eligible patients may need confirmation of food allergy through OFCs before starting treatment.

Despite the numerous studies and the great economic burden of food allergies, little is known regarding the epidemiology of OFCs in the clinical nonresearch setting. Specifically, little is documented about the rate of anaphylaxis and the interventions used in the clinical nonresearch setting for open OFCs in the United States. The current information about OFCs in the United States is based on data collected in research settings along with some studies using data from single center–reported retrospective medical record reviews that consisted of 200 to 1,000 OFCs.[13–18] In these studies, reaction rates were noted to range from 18.8% to 47%, with the following foods being more commonly challenged: peanut, tree nut, and egg.[13–18] In general, the reactions were noted to include oral pruritus and cutaneous symptoms, with an anaphylaxis risk of 6% to 33% of OFCs.[13,15–18] The objective of the study was to describe the epidemiologic profile of clinical open OFCs by reviewing sample data from tertiary clinics across the United States.

Methods

Medical record and literature review was performed in accordance with local institutional review boards. This project obtained data (from January 1, 2008, through December 31, 2013) from 5 of 26 US food allergy centers: Texas Children's Hospital Food Allergy Program (South); University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center (North Midwest); Riley Hospital for Children at Indiana University Health (Midwest); University of Washington School of Medicine, Northwest Asthma & Allergy Center (Northwest); and Boston Children's Hospital (Northeast). Each institution completed a survey with questions assessing the following: (1) number of OFCs performed; (2) number of OFCs with the outcome of anaphylaxis, pruritus, vomiting, hives, facial or tongue swelling, difficulty breathing, changes in blood pressure, or cough; (3) foods challenged in 2013 (milk, baked milk, soy, wheat, peanut, shrimp/shellfish, finned fish, egg, baked egg, tree nut, other); (4) use of an OFC protocol (obtained from the American Academy of Allergy, Asthma, and Immunology Adverse Reactions to Food Committee Work Group Report,[19] PRACTALL consensus report,[20] or other published guidelines); (5) the criteria for a positive reaction; (6) the waiting period after the last dose of an OFC; (7) the use of the prick and prick (the use fresh food items vs standardized extracts) testing method used before OFC; (8) reaction characteristics; (9) the number of challenges in which epinephrine, antihistamines, or steroids was given; and (10) demographics of patients challenged (age, ethnicity, sex, and prior history of food reactions and anaphylaxis). Anaphylaxis was defined according to the criteria outlined by Sampson et al,[21] with some discretion based on clinical judgment of the supervising physician. When a patient developed anaphylaxis based on the criteria of Sampson et al,[21] epinephrine was used for treatment. Although criteria for food challenge

Table 2
Demographics of the Challenged Patients

Demographic	No. (%) of patients by year					
	2008 (n = 790)	2009 (n = 948)	2010 (n = 1,093)	2011 (n = 1,188)	2012 (n = 1,127)	2013 (n = 1,231)
Total Patients						
Male	423 (54)	577 (61)	689 (63)	724 (61)	655 (58)	732 (59)
Age ≤17 years	653 (83)	850 (90)	975 (89)	972 (82)	924 (82)	1,019 (83)
Race						
White	415 (53)	503 (53)	681 (62)	700 (59)	763 (68)	919 (75)
Black	16 (2)	28 (3)	29 (3)	46 (4)	58 (5)	56 (5)
Hispanic	21 (3)	27 (3)	19 (2)	62 (5)	76 (7)	66 (5)
Asian	52 (7)	70 (7)	92 (8)	115 (10)	88 (8)	106 (9)
American Indian	4 (1)	3 (0)	0 (0)	2 (0)	5 (0)	3 (0)
Other	271 (34)	300 (32)	250 (23)	268 (23)	131 (12)	55 (4)
Unknown	10 (1)	16 (2)	21 (2)	1 (0)	4 (0)	25 (2)
Patients with anaphylaxis	13 (2)	8 (1)	14 (1)	11 (1)	14 (1)	33 (3)
Male	9 (69)	6 (75)	11 (79)	9 (82)	9 (64)	24 (73)
Race						
White	10 (77)	6 (75)	7 (50)	9 (82)	11 (79)	30 (91)
Black	0 (0)	1 (13)	1 (7)	1 (9)	1 (7)	0 (0)
Hispanic	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asian	2 (15)	0 (0)	2 (14)	1 (9)	2 (14)	2 (6)
American Indian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	1 (13)	3 (21)	0 (0)	0 (0)	1 (3)
Unknown	1 (8)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)

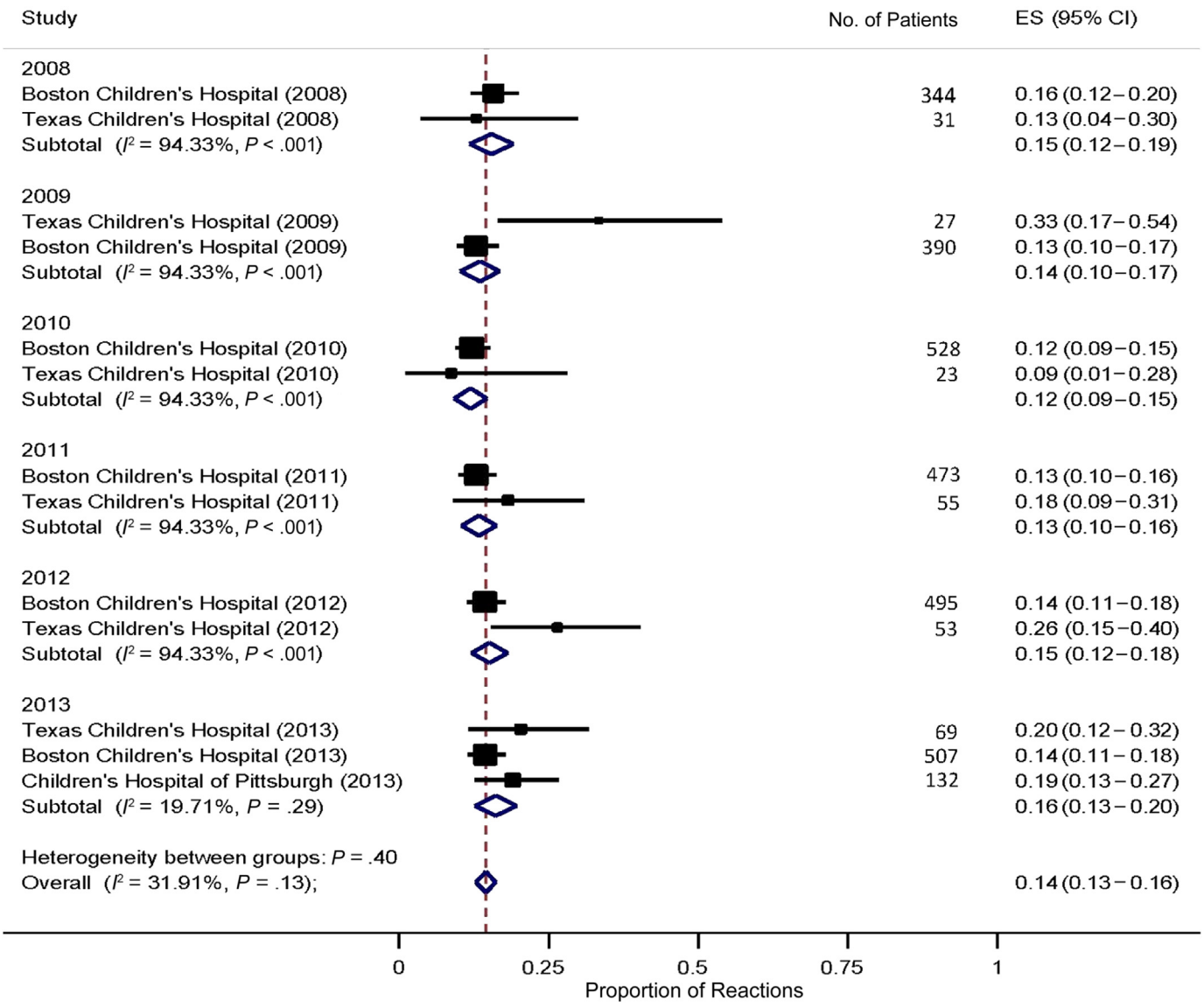

Figure 1. Meta-analysis of reaction rate for oral food challenges per reporting site. The figure shows the proportion of reactions (effect size [ES]) and the 95% confidence interval (CI) for each site within a year, overall for each year, and overall for all years and sites. The meta-analysis weighs sites and years based on amount of data. The size of the squares indicates the weight. Boston Children's Hospital has the highest weight because it has the largest sample size. The I^2 statistic is the percentage of total variation attributable to interstudy heterogeneity.

differed among centers, all centers challenged patients with and without positive skin prick test results. No center only performed challenges on patients with negative skin prick test results. The 95% cutoff values, when available, were used for guidance. One center, Boston Children's Hospital, has reported a quality improvement initiative with food challenges, encompassing some patients also included in this report.[22]

The proportions over time overall and by hospital were determined for the variables listed above. The association among time, hospital, and demographics with reaction rates and anaphylaxis rates were evaluated using a linear mixed model with autoregressive correlation structure that accounted for within hospital correlation. Meta-analysis was used to pool the proportion of reactions, anaphylaxis, epinephrine use, steroid use, and diphenhydramine use by year and overall with inverse-variance weights using a random-effects model with exact confidence intervals (CIs). $P < .05$ was considered statistically significant. All analyses were performed using STATA, version 12.1 (StataCorp, College Station, Texas).

Results

A total of 6,377 open OFCs were performed, with 5,393 of those challenges occurring in patients younger than 18 years. The protocols of the sites are listed in Table 1. The centers report that most OFCs performed were low risk during this study because of one of the following factors: lack of recent reaction, history of tolerance to ingestion, or low levels of specific IgE unless cross-sensitization was suspected. Riley Children's Hospital (Midwest) performed a lower proportion of OFCs in patients younger than 18 years old. Boston Children's Hospital (Northeast) had the largest sample size, whereas Texas Children's Hospital (South) had the smallest sample size. The demographics of the challenged patients are listed in Table 2.

Nonanaphylactic reaction rates ranged from 13% to 33%, depending on year and hospital. There was heterogeneity within all years except 2013 but not between years ($P = .40$), so the overall pooled estimate of the proportion of reactions was appropriate (Fig 1). The pooled estimate of allergic reactions with open OFCs

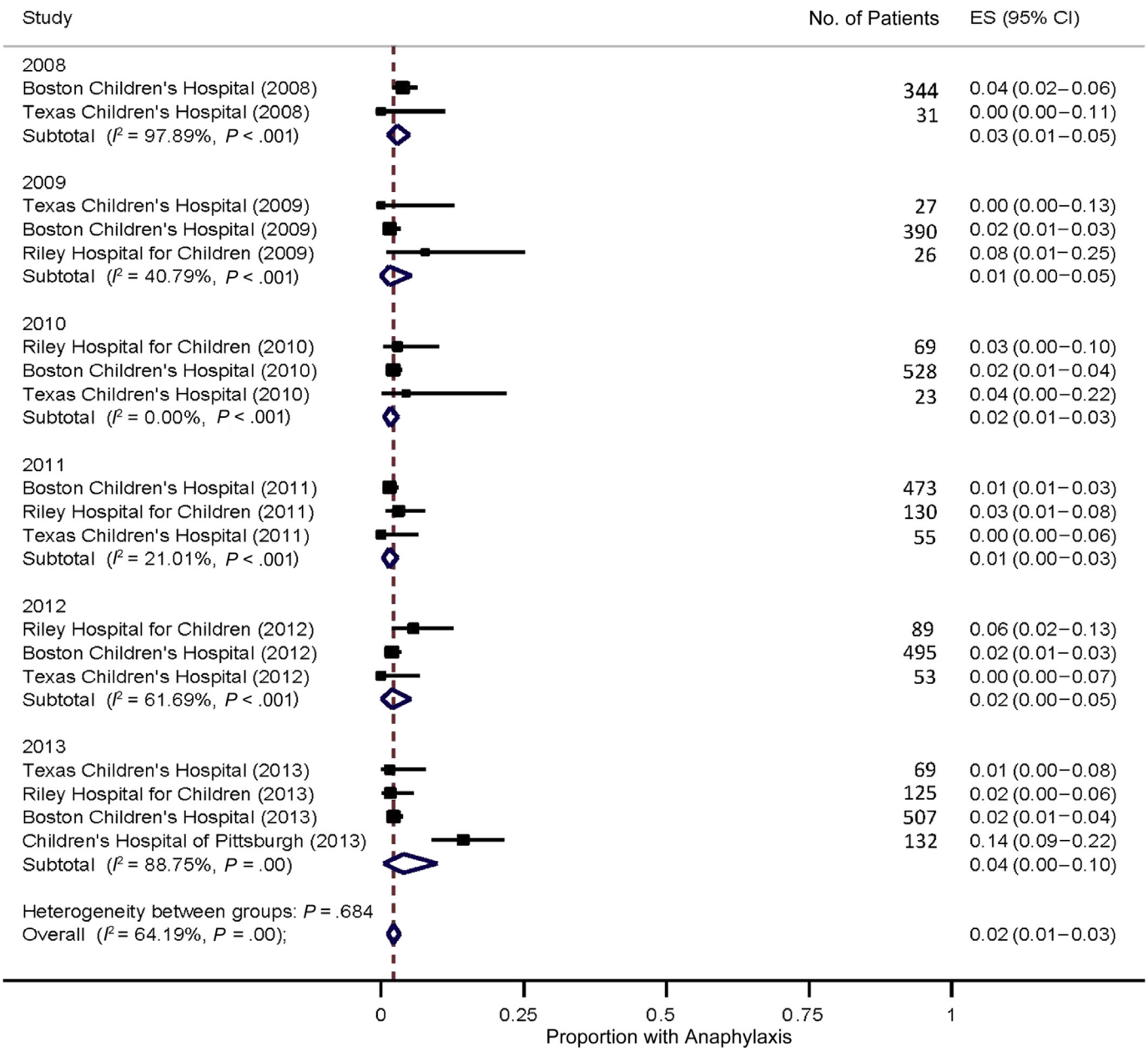

Figure 2. Meta-analysis of anaphylaxis rate for oral food challenges per reporting site. The figure shows the proportion of anaphylaxis (effect size [ES]) and the 95% confidence interval (CI) for each site within a year, overall for each year, and overall for all years and sites. The meta-analysis weighs sites and years based on amount of data. The size of the squares shows the weight. The I^2 statistic is the percentage of total variation attributable to interstudy heterogeneity.

was 14% (95% CI, 13%-16%). The linear mixed-model results indicate that Boston had reaction rate 8.3 percentage points lower than Texas Children's Hospital (95% CI, −10.5 to −6.2; P < .001). The proportion of nonanaphylactic reactions varied significantly from year to year (P = .004). Nonanaphylactic reaction rates were 10.2 percentage points lower in 2010 compared with 2009 (95% CI, −19.0 to −1.4; P = .02), 8.0 points lower in 2011 compared with 2009 (95% CI, −12.8 to −3.3; P = .001), 5.9 points lower in 2013 compared with 2009 (95% CI, −11.7 to −0.2; P = .04), and 7.3 points higher in 2012 compared with 2010 (95% CI, 1.9–12.7; P = .008). Males had a reaction rate that was 16 percentage points higher than females (95% CI, 0.4–37.5; P = .04).

Anaphylaxis rates ranged from 0% to 14%, depending on year and hospital (Fig 2). There was heterogeneity within some years (P < .001 for 2008 and P < .001 for 2013) but not between years (P = .68), so the overall pooled estimate of the proportion of anaphylaxis with OFCs was consistent with each year. The pooled estimate of anaphylaxis was 2% (95% CI, 1%-3%). The linear mixed-model results indicated that centers in the Northeast, Midwest, and North Midwest all had higher proportions of anaphylaxis than the South (P < .001), and centers in the Midwest and North Midwest had higher anaphylaxis rates than the Northeast. The proportion of OFCs that resulted in anaphylaxis did not change over time (P = .45). Just as was seen in nonanaphylactic reaction rates, patients with anaphylaxis were more likely to be males (P = .008) and white (P = .007) compared with patients who did not have anaphylaxis.

Meta-analysis was used to estimate the proportion of treatment (antihistamine, epinephrine, steroids) and 95% CI by year for all OFCs performed (Fig 3A-C). Of the 6,377 OFCs, treatment data were

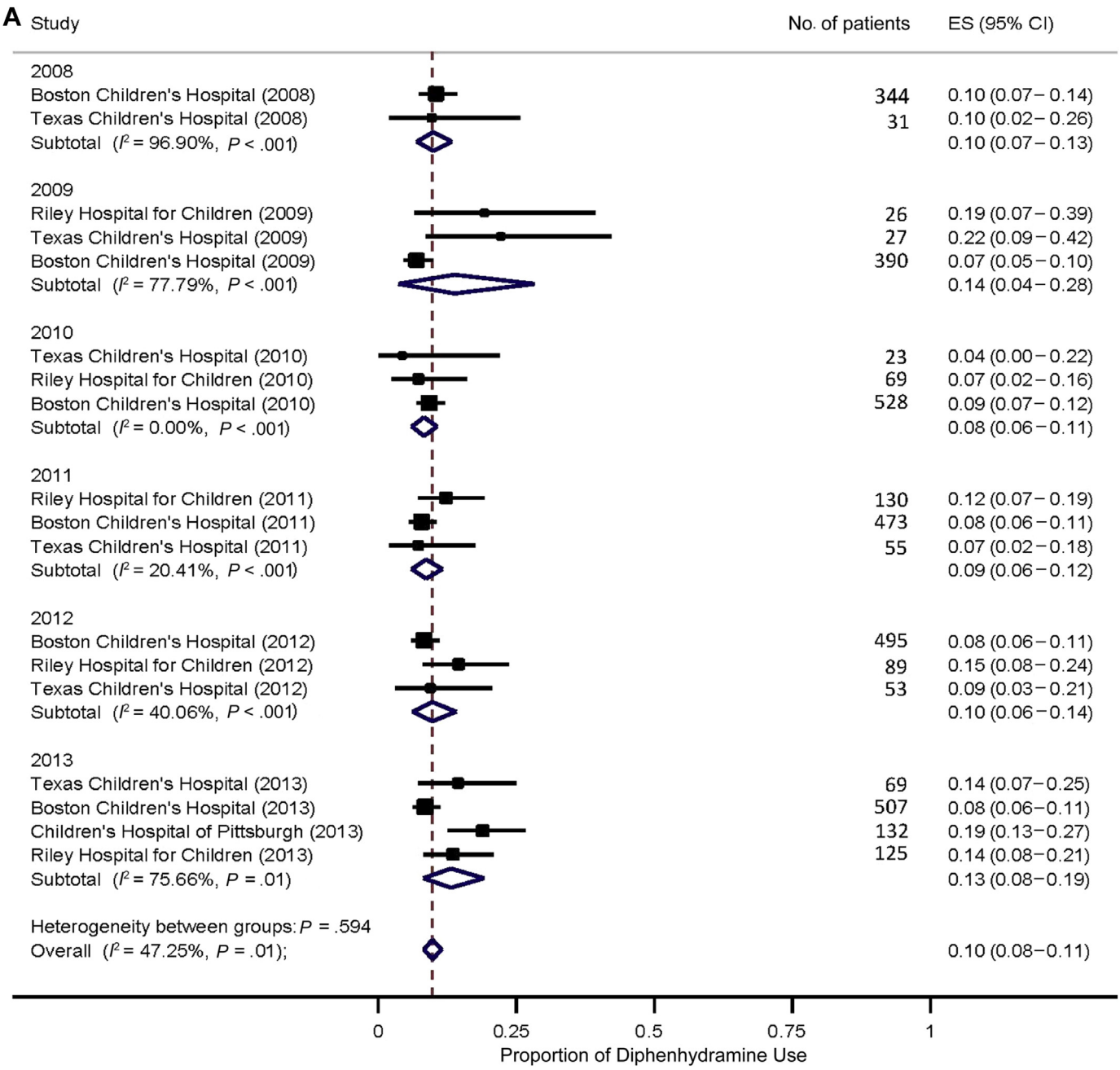

Figure 3. Meta-analyses of treatment interventions for oral food challenges per reporting site. The estimate of the proportion of diphenhydramine, epinephrine, steroids, and given per site and 95% confidence interval (CI) by year is labeled subtotal under each year. The I^2 statistic is the percentage of total variation attributable to interstudy heterogeneity. A, Diphenhydramine; B, epinephrine, and C, steroids.

obtained for 3,127 OFCs. There were 451 of 3,127 challenges that required treatment (14.4%). Antihistamines were used most often when reactions occurred with OFC 76% of the time, whereas epinephrine was used 14% of the time. Steroids were only used 11% of the time. The overall percentage of OFCs that received antihistamines was 10%, and the overall percentages receiving epinephrine and steroids were each 1%.

Figure 4 shows the proportion of hospital admissions that resulted from open OFCs from 2008 to 2013. Nineteen OFCs resulted in patients being placed in hospital observation, and 63 were treated with epinephrine. Hospital admission included all patients who were transferred from the outpatient clinic to an adjacent hospital. Although the exact reason for the admission and the associated challenge food was not determined through the questionnaire, all patients were discharged from the hospital in less than 1 day from admission. The contribution of delayed administration of epinephrine to hospital admission could not be excluded, although all challenges were accompanied by a supervising physician.

The specific foods used for OFCs in 2013 year are shown in Figure 5. There was some variability, but peanuts were universally challenged most across all sites. Texas Children's Hospital (South) challenged egg, baked milk, and peanut at a higher rate. Boston Children's Hospital (Northeast) challenged peanut and egg most often. Riley Hospital for Children (Midwest) challenged peanut and egg, and Pittsburgh (North Midwest) challenged peanut, tree nut,

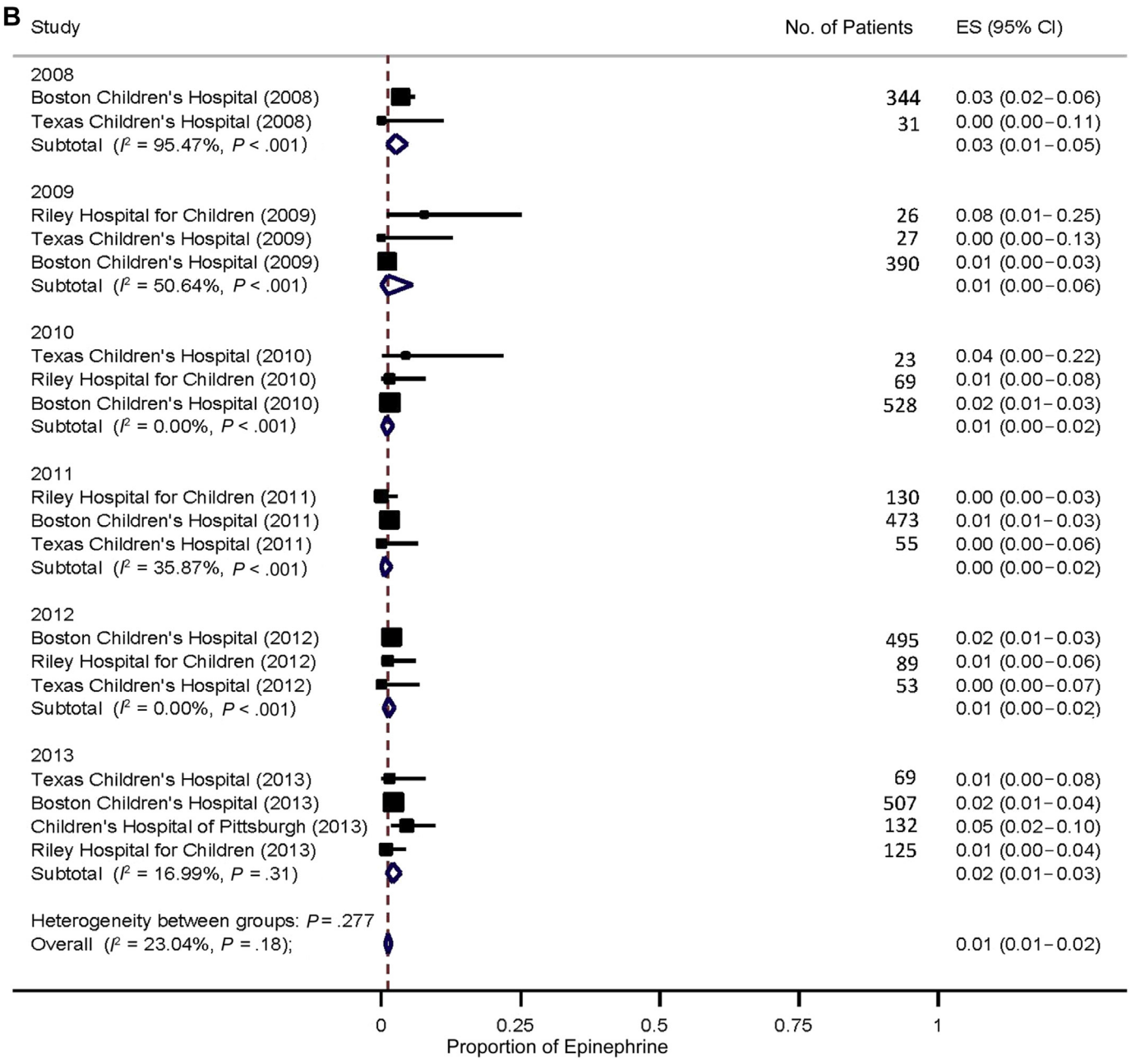

Figure 3. (*continued*).

and milk most often. The most often challenged foods at the Northwest Asthma & Allergy Center (Northwest) were peanut and milk. Texas Children's Hospital (South) challenged more baked milk than the other sites ($P < .001$). The foods from all centers in the other category included oat, chicken, chickpea, kiwi, carrot, lentil, pea, sunflower, sesame seed, rice, banana, turkey, corn, potato, pineapple, strawberry, barley, and kidney bean.

Overall ethnicity over time is shown in Figure 6. For all sites combined, the diversity in the patients with OFCs decreased during the study period, with the proportion of white patients obtaining OFC increasing and the proportion of the other ethnic groups decreasing over time ($P < .001$). Texas Children's Hospital (South) has a higher proportion of challenged patients identified as Hispanic and African American compared with the other sites, whereas Northwest Asthma & Allergy Center (Northwest) had a much higher proportion of patients categorized as belonging to another ethnic group compared with other centers.

Discussion

The prevalence of food allergies has been increasing in the United States.[23] However, not many studies have determined whether this increase is accompanied by increased OFC-proven reaction rates. This study provides data from the largest number of OFCs in 5 geographically distributed locations in the United States. The numbers of overall OFCs performed during a specific period and foods challenged, along with the associated outcomes and interventions, were examined. The severity of OFC reactions in this setting is low, with 2% of OFCs resulting in anaphylaxis and 14% in mild to moderate allergic reactions, requiring no epinephrine.

Food challenges increase the quality of life of food allergic patients,[24] even if they test positive.[25] There is great cost to delaying the performance of OFCs, up to $4,184 per 12 months of delay.[26] Therefore, this procedure should be performed by allergists for appropriate patients with a prior accurate risk assessment per

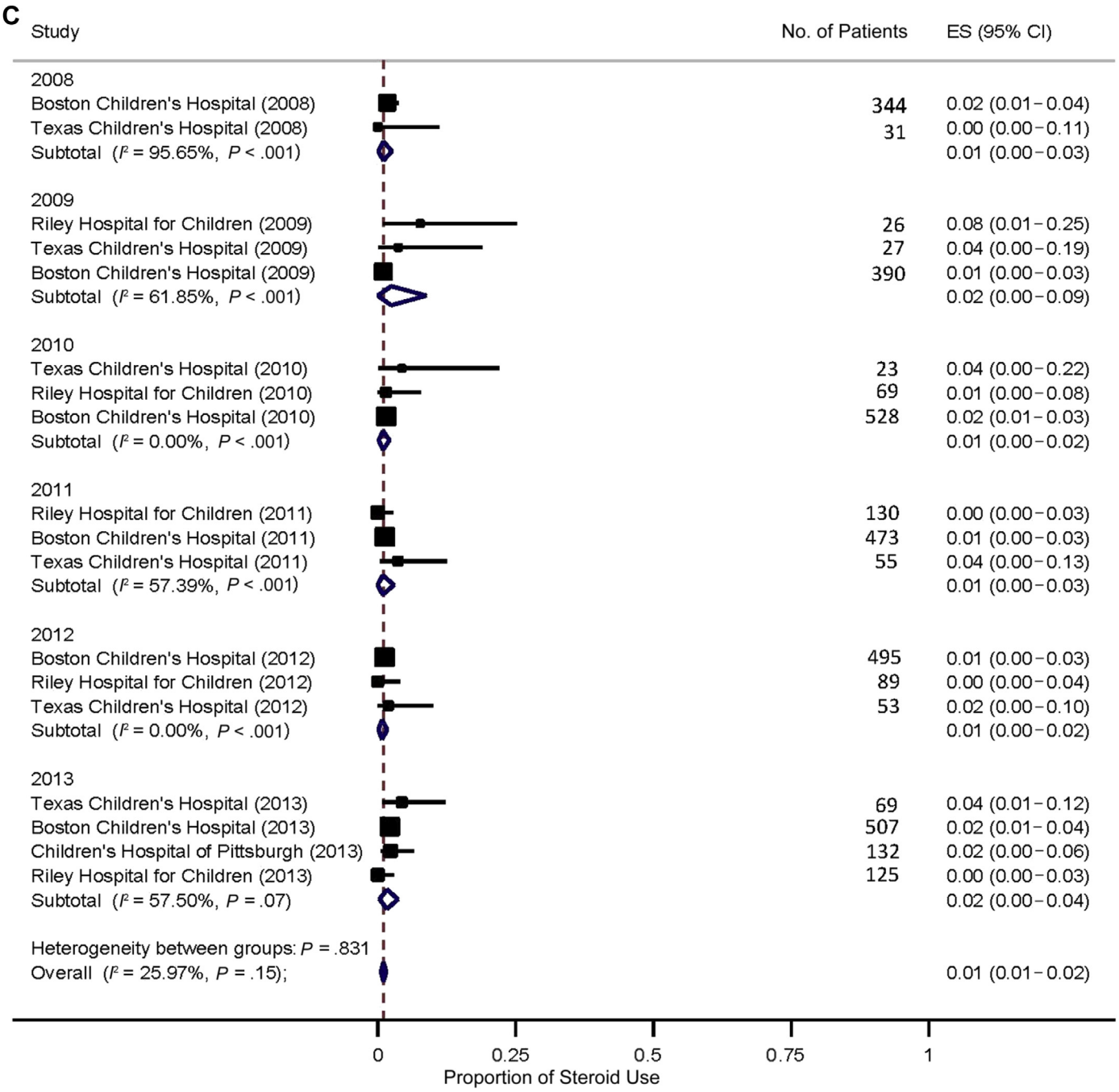

Figure 3. (*continued*).

patient. However, allergists may choose not to perform OFCs in their offices because of perception of risk, time burden, reimbursement concern, and personnel constraints. Therefore, accurate determination of the true risk of OFCs in nonresearch settings is helpful for everyday decision making in clinical practices across the nation. This comprehensive study of a large number of OFCs distributed across the nation estimates the OFC anaphylaxis risk lower than prior studies, which have reported the risk ranging from 6% to 33%.[13–18,27,28] Because OFCs are already considered a safe procedure in allergists' offices, this treatment should be routinely used to maximize quality of life for patients and minimize the economic burden of disease.

Sites participating in the study used different site-specific parameters for their OFCs, including the Practical Allergy (PRACTALL) guidelines,[20] the Adverse Reactions to Food Committee Work Group Report,[19] or practitioner-specific guidelines. The stopping criteria for OFCs in the Work Group Report are descriptive and do not contain specific scoring criteria. The PRACTALL guidelines contain specific scoring criteria with mild, moderate, and severe symptoms of specific target organs scored from 0 to 3. These differences along with the ambiguity in practitioner-specific protocols could account for some of the differences in reaction rates among sites. Most sites incorporated one of the aforementioned guidelines with the exception of Texas Children's Hospital (South) and

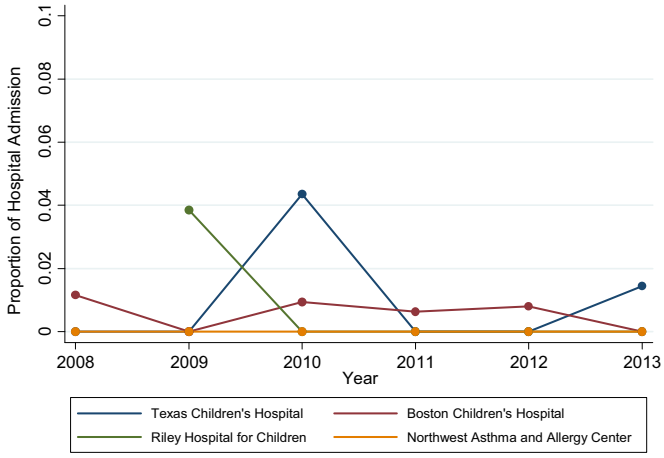

Figure 4. Hospital admissions per total number of food challenges for 2008 to 2013 by reporting hospital.

Northwest Allergy and Asthma Center (Northwest). In each of these sites, the OFC recommendations were used in a combination from 2 of the following protocols: the PRACTALL, the Work Group Report, and/or practitioner-specific parameters. Different dosing regimens may contribute to heterogeneity among sites, but this was not assessed by the survey instrument. Future assessment of the true risk of reaction to OFCs will benefit from a wider acceptance of standardized protocols.

Three of 5 practices in this study performed prick and prick testing to selected foods, mainly fruits and vegetables, before OFC. It is unknown whether this method of testing more accurately predicts OFC outcome compared with skin prick testing with extracts or serum specific IgE. Most practices performed this testing within 6 months of the OFC. In centers that performed prick and prick testing, if results differed from stock extract skin test results performed previously, this may have changed the practitioner's decision to perform the challenge (G.V. and D.R.N., personal communication, 2017). Prick and prick testing of food before OFC has been recommended in the most recent practice parameters as a valid way to determine food allergy for fresh fruits and vegetables or in other foods if extracts are not available.[29]

The pooled data indicate an overall estimated rate of non-anaphylactic reactions of 14% during the study period. Reactions noted in the study population included hives, abdominal pain, shortness of breath, and emesis. These reactions were mild to moderate and most of the time treated with diphenhydramine. Because the rate of these mild reactions that resulted in use of diphenhydramine is approximately 10%, it is reasonable to consider the OFC as a relatively safe procedure. Even though shortness of breath was encountered as a symptom of mild reaction, this is a symptom that, in the absence of wheezing, cough, or stridor, could be subjective and is not considered a severe symptom by the PRACTALL guidelines.[20] Although shortness of breath would indicate respiratory difficulty (a criterion for the definition of anaphylaxis),[21] this was not classified as severe in some cases. This highlights some of the ambiguity of determining the severity of OFC reactions.

The pooled meta-analysis of the data provided by the 4 sites (partial data were collected from one site and in turn were not included in meta-analysis) indicates a 2% rate of anaphylaxis during the 2008–2013 study period, with a 95% CI of 1% to 3% for OFCs performed in the clinical nonresearch setting. This finding is similar to reported rates in countries outside the United States.[30] The perceived safety concern for performing OFCs in the nonresearch clinical setting at first glance is supported by the pooled rate of anaphylaxis occurring during nonresearch clinical OFCs performed in our population being higher than the reported rate of anaphylaxis seen in immunotherapy systemic reactions performed in US allergy clinics.[31] However, when one considers that the rate of

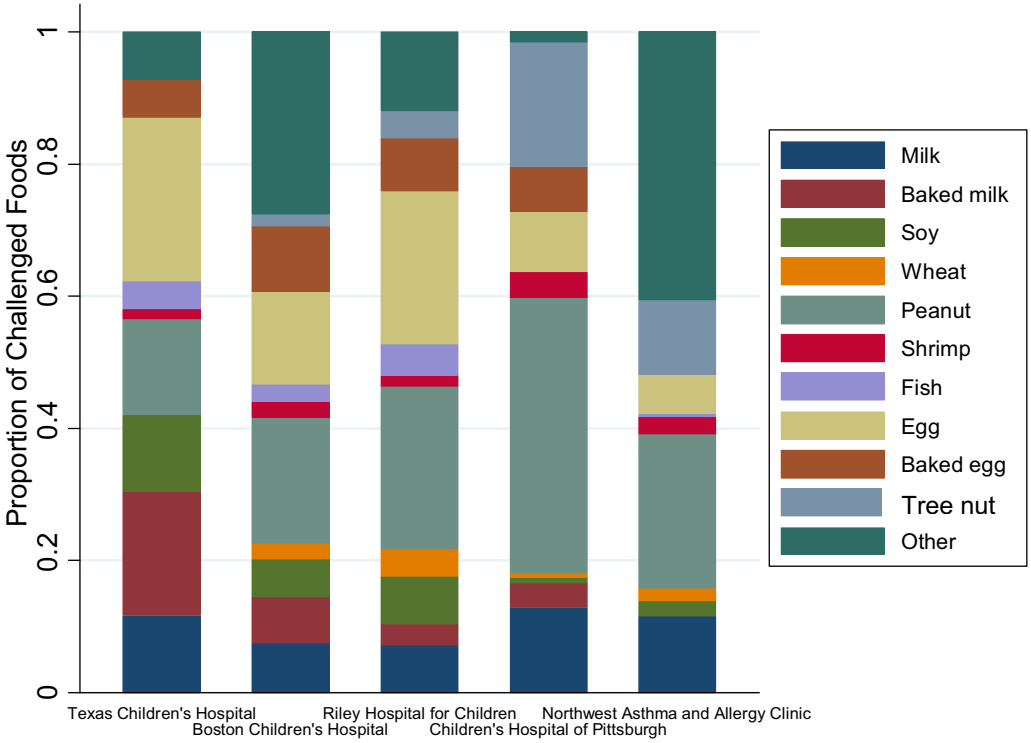

Figure 5. Proportion of foods challenged in 2013 by hospital.

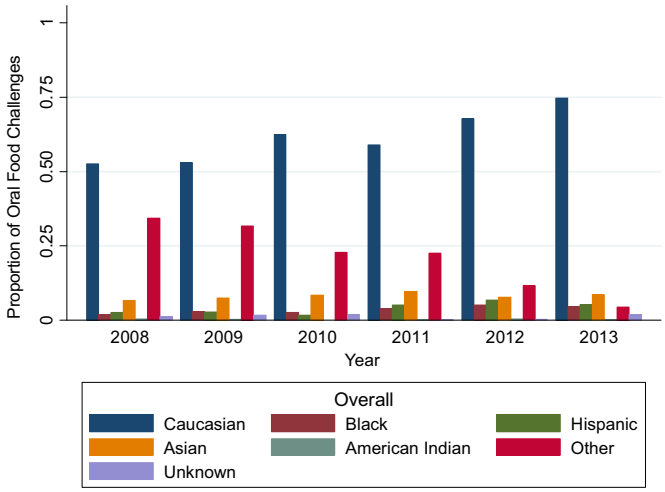

Figure 6. Oral food challenges by patient race/ethnicity from 2008 to 2013.

anaphylaxis for a single OFC may be higher than a single allergy shot provided during immunotherapy, the rate of anaphylaxis across a full course of immunotherapy (up to 100 visits) is comparable to that of a food challenge. Therefore, because allergists are skilled at treating anaphylaxis, they should feel comfortable performing OFCs. Because allergists perform drug challenges and aeroallergen immunotherapy routinely, we believe the allergist's office is best equipped with the expertise and staff to perform clinical OFCs. Although up to 85% of allergists report they perform OFCs, only 5.6% of allergists perform more than 10 OFCs per month and 70% perform only 1 to 5 OFCs per month, with risk of an adverse event cited as 1 of the top 3 barriers.[32] Allergists should perform this practice on a regular basis to ensure patients do not needlessly avoid foods for fear of allergic reactions and thus subsequently live with the anxiety related to avoidance. Furthermore, the risk of anaphylaxis should be evaluated with prospective epidemiologic studies.

Although late-phase and biphasic reactions were not assessed with this survey, prior studies have found that the rate of these reactions during OFC ranges from 1.5% to 4%.[13,33,34] A subset of patients who experience anaphylaxis and are treated with epinephrine during OFC have biphasic reactions. Features associated with biphasic reactions include multiple organ involvement, more severe reactions, and multiple doses of epinephrine. The rate of anaphylaxis of 2% from this survey and the 1% (n = 63/6377) of patients requiring epinephrine after OFC suggests biphasic responses would not have occurred in this study more often than what has been previously reported.

The assessment of the specific food allergens used for OFCs for the 2013 year found that for most sites milk, peanut, or egg were consistently challenged most and were associated with an increased rate of positive reactions compared with other foods challenged. This observation is consistent with the known epidemiology of milk, peanut, and egg as the most common food allergens.[2] Many of the sites were noted to have a number of open OFCs to baked foods (milk or egg). In particular, Texas Children's Hospital (South) had a higher rate of baked milk challenges, whereas Boston Children's Hospital (Northeast) had a higher rate of baked egg challenges. This observation is explained by the trend to attempt to increase the dietary options for people with known milk and egg allergies by testing for ability to tolerate baked products. The introduction of baked milk and egg products may have some benefit for hastening tolerance development to milk and egg in children with allergic disease[35,36] and should be considered as an intervention in cases where tolerance to baked goods is unknown.

The predominance of male patients with more reactions is consistent with the observation of more frequent food allergic disease in males.[37] During this time, most patients undergoing OFCs at all sites participating were white. Even though the absolute number of black and Hispanic patients who underwent OFCs increased during the survey period, the proportion of whites undergoing OFCs increased compared with the other ethnic groups. This finding suggests a decrease in diversity in patients challenged from 2008 to 2013. This was noted most prominently at the Texas Children's Hospital (South) site location, where the regional population almost doubled during the 6-year period. Given the observation that minority populations more often have symptoms when surveyed by telephone or National Health and Nutrition Examination Surveys,[2,38] it is especially important for allergists treating minority patients to offer OFC procedures to these patients. Patients may be more at risk of developing allergic reactions from unintentional exposures if the diagnosis of food allergy is unclear.

The limitations of this study included the inability to collect more robust data (including specific IgE values) because of electronic medical record upgrades at some sites, to determine biphasic responses in a systematic fashion, and to determine the complete epidemiologic picture of food allergies based on only a few centers, although these centers represent a snapshot of different regions of the country. There may also be limitations on the generalization of results to private practice settings because all sites were tertiary academic institutions with resource-rich environments. Another potential limitation is the lack of differentiation between IgE-mediated OFCs vs non–IgE-mediated OFCs. Therefore, resulting reactions may be misclassified, and the rate of anaphylaxis underestimated or overestimated. However, the number of challenges performed for other than IgE-mediated reactions is likely to be small and, therefore, unlikely to substantially alter the results. Finally, uniform criteria for recommending OFC varied among locations, making comparisons imperfect and limiting generalizability.

This is the largest assessment of allergic reactions to clinical OFCs in the United States to date. Studies from outside the United States have used OFCs in the context of evaluating disease progression for specific food allergens (ie, peanut)[39] or to diagnose food allergy for research protocols.[40] In the United States, previous studies have been single-center studies with determination of reaction rates of OFCs in an office setting located in one geographic area[14,15] or single-center studies determining reaction rates of OFCs in the context of clinical research protocols.[13] This study is the first study, to our knowledge, to evaluate OFC reactions in 5 widely geographically distributed centers, which clarifies the risk of performing clinical nonresearch open OFCs. OFCs are a safe procedure and should be performed by practicing allergists when indicated. Allergists are the most capable physicians to evaluate and manage this risk.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anai.2017.07.028.

References

[1] Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. *J Allergy Clin Immunol*. 2010;126:1105–1118.
[2] McGowan EC, Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007-2010. *J Allergy Clin Immunol*. 2013;132:1216–1219.e5.
[3] Dyer AA, Gupta R. Epidemiology of childhood food allergy. *Pediatr Ann*. 2013;42:91–95.

[4] Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. *JAMA Pediatr*. 2013;167:1026–1031.
[5] Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. *Ann Allergy Asthma Immunol*. 2001;87:461–464.
[6] Robbins KA, Wood RA, Keet CA. Milk allergy is associated with decreased growth in US children. *J Allergy Clin Immunol*. 2014;134:1466–1468.e6.
[7] Wood RA. Food allergen immunotherapy: current status and prospects for the future. *J Allergy Clin Immunol*. 2016;137:973–982.
[8] Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol*. 2014;133:468–475.
[9] Vickery BP, Lin J, Kulis M, et al. Peanut oral immunotherapy modifies IgE and IgG4 responses to major peanut allergens. *J Allergy Clin Immunol*. 2013;131:128–134.e1-e3.
[10] Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol*. 2015;135:1275–1282.e1-e6.
[11] Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol*. 2012;129:448–455. 455, e1-e5.
[12] Jones SM, Burks AW, Dupont C. State of the art on food allergen immunotherapy: oral, sublingual, and epicutaneous. *J Allergy Clin Immunol*. 2014;133:318–323.
[13] Noone S, Ross J, Sampson HA, Wang J. Epinephrine use in positive oral food challenges performed as a screening test for food allergy therapy trials. *J Allergy Clin Immunol Pract*. 2015;3:424–428.
[14] Lieberman JA, Cox AL, Vitale M, Sampson HA. Outcomes of office-based, open food challenges in the management of food allergy. *J Allergy Clin Immunol*. 2011;128:1120–1122.
[15] Perry TT, Matsui EC, Conover-Walker MK, Wood RA. Risk of oral food challenges. *J Allergy Clin Immunol*. 2004;114:1164–1168.
[16] Ram G, Cianferoni A, Spergel JM. Food allergy to uncommonly challenged foods is rare based on oral food challenge. *J Allergy Clin Immunol Pract*. 2016;4:156–157.e5.
[17] Cianferoni A, Garrett JP, Naimi DR, Khullar K, Spergel JM. Predictive values for food challenge-induced severe reactions: development of a simple food challenge score. *Isr Med Assoc J*. 2012;14:24–28.
[18] Fleischer DM, Bock SA, Spears GC, et al. Oral food challenges in children with a diagnosis of food allergy. *J Pediatr*. 2011;158:578–583.e1.
[19] Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, et al. Work Group report: oral food challenge testing. *J Allergy Clin Immunol*. 2009;123:S365–S383.
[20] Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130:1260–1274.
[21] Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–397.
[22] Simberloff T, Parambi R, Bartnikas LM, et al. Implementation of a Standardized Clinical Assessment and Management Plan (SCAMP) for Food Challenges. *J Allergy Clin Immunol Pract*. 2017;5:335–344.e3.
[23] Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128:e9–e17.
[24] van der Velde JL, Flokstra-de Blok BM, de Groot H, et al. Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children. *J Allergy Clin Immunol*. 2012;130:1136–1143.e2.
[25] DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire–Parent Form in children 0-12 years following positive and negative food challenges. *Clin Exp Allergy*. 2010;40:476–485.
[26] Couch C, Franxman T, Greenhawt M. The economic effect and outcome of delaying oral food challenges. *Ann Allergy Asthma Immunol*. 2016;116:420–424.
[27] DunnGalvin A, Segal LM, Clarke A, Alizadehfar R, Hourihane JO. Validation of the Cork-Southampton Food Challenge Outcome Calculator in a Canadian sample. *J Allergy Clin Immunol*. 2013;131:230–232.
[28] DunnGalvin A, Daly D, Cullinane C, et al. Highly accurate prediction of food challenge outcome using routinely available clinical data. *J Allergy Clin Immunol*. 2011;127:633–639.e1-e3.
[29] Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update–2014. *J Allergy Clin Immunol*. 2014;134:1016–1025.e43.
[30] Calvani M, Berti I, Fiocchi A, et al. Oral food challenge: safety, adherence to guidelines and predictive value of skin prick testing. *Pediatr Allergy Immunol*. 2012;23:755–761.
[31] Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, year 3: what practices modify the risk of systemic reactions? *Ann Allergy Asthma Immunol*. 2013;110:274–278.e1.
[32] Pongracic JA, Bock SA, Sicherer SH. Oral food challenge practices among allergists in the United States. *J Allergy Clin Immunol*. 2012;129:564–566.
[33] Järvinen KM, Amalanayagam S, Shreffler WG, et al. Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children. *J Allergy Clin Immunol*. 2009;124:1267–1272.
[34] Lee J, Garrett JP, Brown-Whitehorn T, Spergel JM. Biphasic reactions in children undergoing oral food challenges. *Allergy Asthma Proc*. 2013;34:220–226.
[35] Leonard SA. Debates in allergy medicine: baked milk and egg ingestion accelerates resolution of milk and egg allergy. *World Allergy Org J*. 2016;9:1.
[36] Leonard SA, Caubet JC, Kim JS, Groetch M, Nowak-Wegrzyn A. Baked milk-and egg-containing diet in the management of milk and egg allergy. *J Allergy Clin Immunol Pract*. 2015;3:13–23.
[37] Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014;133:291–307.
[38] Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol*. 2010;126:798–806.e13.
[39] Nicolaou N, Poorafshar M, Murray C, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol*. 2010;125:191–197.e1-e13.
[40] Osborne NJ, Koplin JJ, Martin PE, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol*. 2011;127:668–676.e1-e2.

Supplementary Data

Please answer following questions for years 2008–2013 unless otherwise specified in the question.

1. How many food challenges were performed during each year at your center? (Please fill answers in the Table below)
   a. How many were ages ≤17?
   b. How many were males?
   c. How many were Caucasian?
   d. How many were African American/Black?
   e. How many were Hispanic or of Latino descent?
   f. How many were Asian?
   g. How many were American Indian or Alaska Native?
   h. How many were classified as other?
2. How many patients developed anaphylaxis during the food challenges during each year at your center? (Please fill answers in the Table below)
   a. How many were ages ≤17?
   b. How many were males?
   c. How many were Caucasian?
   d. How many were African American/Black?
   e. How many were Hispanic or of Latino descent?
   f. How many were Asian?
   g. How many were American Indian or Alaska Native?
   h. How many were classified as other?
3. Does your institution use center specific guidelines for food challenges? (Please circle one)
   Yes No
4. If so, which of the following are used for the guidelines?(Please circle one)
   a. PRACTALL Consensus report
   b. Oral work group report
   c. Other published guidelines
   d. Provider specific parameters are used.
5. What is the observation period after the last dose of food is ingested for a food challenge at your institution?
6. Is Prick & Prick testing used prior to oral food challenges at your institution? (Please circle one)
   Yes No
7. What number of challenges resulted in the use of epinephrine?
8. What number of challenges resulted in the use of diphenhydramine?
9. What number of challenges resulted in the use of steroids?
10. What number of challenges resulted in patient being admitted for oberservation?
    a. How many of the above challenges spent ≤1 day in the Hospital?

Please answer the following questions for the year 2013:

5. How many patients were noted to have a reaction during an oral food challenge per your institutional parameters?
6. How many patients were challenged to milk?
   b. How many of those patients had an allergic reaction?
7. How many patients were challenged to soy?
   c. How many of those patients had an allergic reaction?
8. How many patients were challenged to wheat?
   d. How many of those patients had an allergic reaction?
9. How many patients were challenged to peanuts?
   a. How many of those patients had an allergic reaction?
10. How many patients were challenged to shrimp?
    a. How many of those patients had an allergic reaction?
11. How many patients were challenged to flat fish?
    a. How many of those patients had an allergic reaction?
12. How many patients were challenged to shell fish?
    a. How many of those patients had an allergic reaction?
13. How many patients were challenged to eggs?
    a. How many of those patients had an allergic reaction?
14. How many patients were challenged to tree nuts?
    a. How many of those patients had an allergic reaction?

Year	2008	2009	2010	2011	2012	2013
Total Number of Food Challenges						
Number of Challenged Patients who are:						
a)Male						
b)Caucasian						
c) African American/Black						
d) Hispanic or of Latino descent						
e) Asian						
f) American Indian/Alaska Native						
g) Other						
Number of Challenged Patients with Anaphylaxis who are:						
a)Male						
b)Caucasian						
c) African American/Black						
d) Hispanic or of Latino descent						
e) Asian						
f) American Indian/Alaska Native						
g) Other						
Treatment						
Number of positive challenges with						
a. Epinephrine use						
b. Diphenhydramine use						
c. Steroid use						
Number of Challenges Admitted						