



It's a rash: Antibiotic allergies in the modern era of antibiotic stewardship

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ABSTRACT

Objectives: To determine whether current guidelines emphasizing antibiotic stewardship in pediatrics have been associated with reduced prevalence of antibiotic allergies in children severely affected by otitis media undergoing bilateral myringotomy with tympanostomy tube insertion (BMT) or by recurrent sinusitis or adenotonsillitis undergoing adenoidectomy with or without tonsillectomy.

Methods: Case series of consecutive patients undergoing BMT or adenoidectomy with/without tonsillectomy for recurrent acute otitis media, recurrent sinusitis, or recurrent tonsillitis during November 2008 or November 2017 at a tertiary care children's hospital. Children with primarily obstructive indications for surgery, with prior tube placement or adenoidectomy, or with surgery by an outside provider were excluded. Demographics, type of surgery, and allergies or allergic symptoms were collected from the electronic medical record. Factors associated with antibiotic allergies were compared using logistic regression, Wilcoxon rank-sum, or Chi-squared test.

Results: Seventy-five children who underwent surgery during 2008 and 75 children who underwent surgery in 2017 were included. Overall, median age at surgery was 3.24 years (range 0.56–17.49 years). Seventy-nine (52.7%) patients were female and 95 (63.3%) had private insurance. BMT was the most common surgery (82 children, 54.7%) followed by tonsillectomy with adenoidectomy (46 children, 30.7%), and adenoidectomy without tonsillectomy (39 children, 26.0%). Symptoms of allergic rhinitis were reported by 53 (35.3%) patients, and 11 (7.3%) and 5 (3.3%) had positive environmental and food allergy testing, respectively. Surprisingly, there was not a significant difference between the prevalence of antibiotic allergies in patients undergoing surgery during 2017 (17 patients, 22.7%) compared with 2008 (14 patients, 18.7%) (OR: 1.28, 95% CI: 0.578–2.82, $p = 0.546$). However, antibiotic allergies were less common in females (OR: 0.413, 95% CI: 0.182–0.937, $p = 0.034$) and more common in patients with a family history of antibiotic allergies (OR: 36.9, 95% CI: 5.12– ∞ , $p < 0.001$). **Conclusion:** Pediatric otolaryngology surgical patients continue to exhibit a similar and high prevalence of antibiotic allergies in 2017 compared with 2008. Future studies are needed to determine whether this is because of overdiagnosis of antibiotic allergies or a failure of antibiotic guideline adherence to reduce antibiotic allergy prevalence.

1. Introduction

The American Academy of Pediatrics (AAP), Centers for Disease Control (CDC), Infectious Disease Society of America (IDSA), and World Health Organization (WHO) all developed evidence-based clinical guidelines for appropriate antibiotic use for pediatric bacterial otitis media, sinusitis, and tonsillitis [1–4]. Since the 1990s, antibiotic resistance stemming from antibiotic use and overuse has been heralded one of the greatest public health risks of our time [5]. In addition to resistance, the long-term deleterious impact of early antibiotic exposure on

the infant microbiome is now recognized, including obesity [6], asthma [7], allergies [8], and chronic illnesses such as inflammatory bowel disease [9–12].

More specific to this study is the major public health concern of high antibiotic allergy rates in children. Over-prescription of antibiotics has been hypothesized to contribute to the prevalence of antibiotic allergies [13], suggesting that the prevalence of antibiotic allergies may serve as a surrogate measure of antibiotic use. Limited antibiotic choices due to allergy coupled to a dearth of development of new alternatives have experts very concerned about the future [14–16]. Furthermore,

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antibiotic allergies restrict the armamentarium of antibiotic choices often forcing providers to empirically prescribe options that exhibit a much broader spectrum than what is needed which in turn potentially selects resistant clones [3].

Children with refractory or recurrent infections require bilateral myringotomy with tubes (BMT) for otitis media and adenoidectomy with or without tonsillectomy for pharyngotonsillitis or adenoiditis/sinusitis. Children undergoing these surgeries have been treated with multiple courses of antibiotics, often at a very young age, prior to otolaryngology referral. Evidence-based guidelines and implementation of antibiotic stewardship programs have reduced antibiotic use and early exposure [17–22] but there is no published literature to date specifically evaluating these “severely affected” patients who qualify for surgery. Therefore, the number of patients who underwent BMT or adenoidectomy with or without tonsillectomy with antibiotic allergies in 2008 as compared with 2017 was evaluated. We hypothesized that changes in prescribing patterns would result in a decreased prevalence of antibiotic allergies in 2017 compared with 2008.

2. Methods

2.1. Patients

Following approval from the University of Pittsburgh Institutional Review Board, patients undergoing BMT or adenoidectomy with/without tonsillectomy at a tertiary care children’s hospital were identified from perioperative administrative records. November 2008 was selected as the historical cohort because they were the earliest records available in the perioperative database. November 2017 was selected as the more recent cohort. Inclusion criteria comprised undergoing one or more of the surgeries listed above for recurrent acute otitis media, recurrent sinusitis, or recurrent tonsillitis. Children with primarily obstructive indications for surgery; those with prior tube placement or adenoidectomy; and those with BMT, adenoidectomy, or tonsillectomy by an outside provider were excluded.

2.2. Data collection

Demographics (sex, race, median household income for zip code, and presence of private insurance), type of surgery (BMT, adenoidectomy, or tonsillectomy and adenoidectomy), age at surgery, allergies or allergic symptoms (parent-reported symptoms of allergic rhinitis, results of environmental allergy testing, and results of food allergy testing), and other pertinent medical history (immunodeficiency, Down syndrome, cleft palate, submucous cleft palate, and immunization status) were collected from clinic and operative notes as well as parent questionnaires completed at Otolaryngology clinic visits. Family history of antibiotic allergies and environmental protective or risk factors (duration of breast milk feeding and smoke and pet exposure) were collected from parent questionnaires. Allergy alerts in the electronic medical record and Allergy & Immunology and Otolaryngology clinic notes were reviewed for antibiotic allergies; type of antibiotic and reaction were recorded.

2.3. Statistical analysis

Categorical data were summarized as n (%). Data for all continuous variables were not normally distributed (Shapiro-Wilk $p < 0.05$) and were summarized as median (range). Differences in patients with and without antibiotic allergies and between patients in the two groups (2008 and 2017) were assessed using exact or standard logistic regression for dichotomous variables and Wilcoxon rank-sum for continuous variables. In addition, birth years were categorized so that approximately 25% of the patients fell in each group (1991–2005, 2006–2007, 2008–2014 and 2015–2017) and the impact of birth year on the prevalence of antibiotic allergies was assessed using the Chi-squared test. All

statistical analyses were conducted using Stata/SE 16.0 (StataCorp, College Station, Tx), and $p < 0.05$ was considered significant.

The main outcome measure was the prevalence of antibiotic allergies in 2017 compared with 2008. A power analysis was performed based on preliminary data in which 7/51 (13.7%) children from 2008 had antibiotic allergies compared with 6/51 (11.8%) children from a more recent year. With power = 0.80, and $\alpha = 0.05$, this analysis revealed that a total of 9674 patients, (4837 in each year) would be required to detect a significant difference in antibiotic allergy prevalence.

3. Results

3.1. Demographics and surgical details

After review of 357 charts, 75 children who underwent surgery during 2008 and 75 children who underwent surgery in 2017 were included. Two-hundred and seven patients met exclusion criteria. Data collection was terminated because there was no trend toward a significant difference between the prevalence of antibiotic allergies in patients undergoing surgery during 2017 (17 patients, 22.7%) compared with 2008 (14 patients, 18.7%) (OR: 1.28, 95% CI: 0.578–2.82, $p = 0.546$) (Fig. 1). In addition, when patients undergoing BMT, tonsillectomy with adenoidectomy, and adenoidectomy without tonsillectomy were examined separately, there continued to be no significant difference in the prevalence of antibiotic allergies in 2017 compared with 2008 in any subsets (Fig. 1). Overall, median age at surgery was 3.24 years (range 0.56–17.49 years) (Table 1). Seventy-nine (52.7%) patients were female and 95 (63.3%) had private insurance. None were Hispanic. BMT was the most common surgery (82 children, 54.7%) followed by tonsillectomy with adenoidectomy (46 children, 30.7%), and adenoidectomy without tonsillectomy (39 children, 26.0%) (Fig. 2).

3.2. Risk factors

Potential risk or protective factors for recurrent infections or allergies are summarized in Fig. 3. Symptoms of allergic rhinitis were reported for 53 (35.3%) patients, and 11 (7.3%) and 5 (3.3%) had positive environmental and food allergy testing, respectively. Seventy-seven of the 140 patients with completed parent questionnaires received some breast milk. Of these 77, 61 parents reported duration of breast milk feeding, with a median of 6 months (range 0.25–48 months) (Table 1).

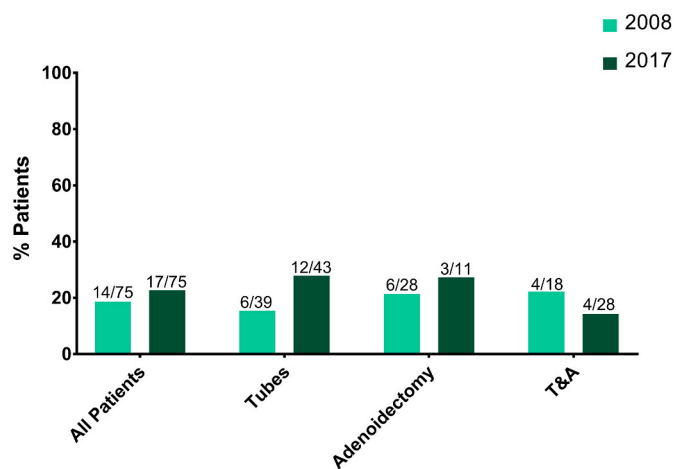


Fig. 1. Prevalence of antibiotic allergies in 2008 and in 2017 in all patients and in subsets undergoing tubes, adenoidectomy without tonsillectomy, or tonsillectomy and adenoidectomy (T&A).

Table 1
Continuous patient characteristics.

	Median	Range
Median Household Income	\$52,318.5	\$15,057–\$129,063
Months of Breast Milk (n = 61)	6	0.25–48
Years of Age at Surgery	3.24	0.56–17.49

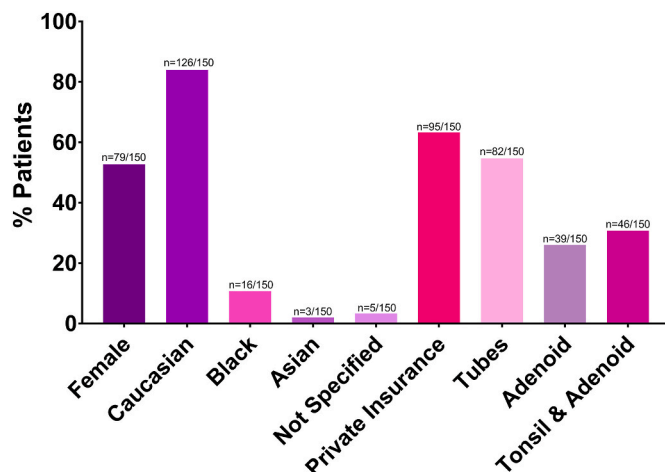


Fig. 2. Demographics and surgery type. Abbreviations: T&A: Tonsillectomy and adenoidectomy; Pos: Positive; Env: Environmental; Hx: History.

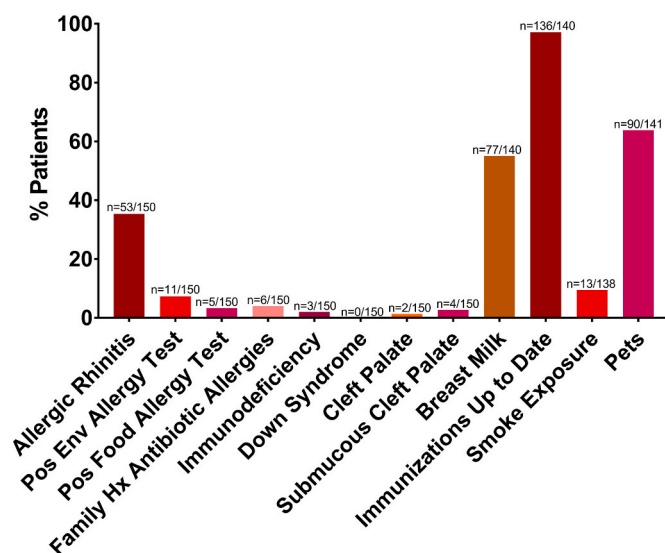


Fig. 3. Potential risk factors for recurrent infections and allergies.

3.3. Antibiotic allergies

Thirty-one (20.7%) patients had parent-reported antibiotic allergies, mostly to penicillin beta-lactam antibiotics (penicillin, amoxicillin, or amoxicillin-clavulanate; 26/31). Other allergies were to cephalosporins (cefдинir and ceftriaxone; 4/31), macrolides/azalides (azithromycin; 3/31), sulfonamides (sulfamethoxazole/trimethoprim; 3/31), and lincosamides (clindamycin; 1/31). Five children had parent-reported allergies to multiple antibiotics. Reactions were documented for 21 patients. Thirteen parents reported only rashes/hives; four reported only gastrointestinal complications; one reported swelling of the hands and feet; one reported throat closing as well as a rash; one reported hives, extreme fatigue, and vomiting; and one reported rashes, hives, and

gastrointestinal complications. Only one patient underwent allergy testing; this patient's parent reported an allergic reaction to amoxicillin at 18 months of age but the patient had a successful oral challenge at eight years of age.

3.4. Comparing patients with and without antibiotic allergies

Antibiotic allergies were less common in females (OR: 0.413, 95% CI: 0.182–0.937, $p = 0.034$) and more common in patients with a family history of antibiotic allergies (OR: 36.9, 95% CI: 5.12– ∞ , $p < 0.001$) (Fig. 4). In addition, year of birth did not have a significant impact on prevalence of antibiotic allergies; antibiotic allergies were present in 9/30 (30.0%), 6/38 (15.8%), 6/32 (18.8%), and 10/35 (28.6%) of those born in 1991–2005, 2006–2007, 2008–2014, and 2015–2017, respectively. No other demographic or risk factors were associated with antibiotic allergies.

3.5. Comparing patients with surgery in 2008 and 2017

Demographic characteristics and risk factors were further compared between patients with surgery in 2008 and those with surgery in 2017 (Fig. 5). As expected, receiving breast milk (OR: 2.00, 95% CI: 1.02–3.93, $p = 0.044$) was more common in 2017. However, fewer patients in 2017 were African American (OR: 0.122, 95% CI: 0.0266–0.558, $p = 0.007$) or reported allergic rhinitis symptoms (OR: 0.361, 95% CI: 0.180–0.725, $p = 0.004$) or smoke exposure (OR: 0.157, 95% CI: 0.0335–0.739, $p = 0.019$) compared with 2008. When these factors were incorporated in a multivariable logistic regression model, year of surgery was still not significantly associated with antibiotic allergies (Table 2). Separate multivariable logistic regressions were also performed for subsets of patients with each surgery type; again, year of surgery was not significantly associated with antibiotic allergies (Table 2).

4. Discussion

Early antibiotic use alters gut microbiome diversity and predisposes children to obesity, asthma, allergies, and other inflammatory disorders [6,7,9–12]. Concerns regarding these negative long-term sequelae and antibiotic resistance have spurred guidelines for limiting pediatric antibiotic prescriptions and the implementation of antibiotic stewardship programs throughout the country [21,22]. Despite evidence that these programs have reduced unnecessary antibiotic use, we were

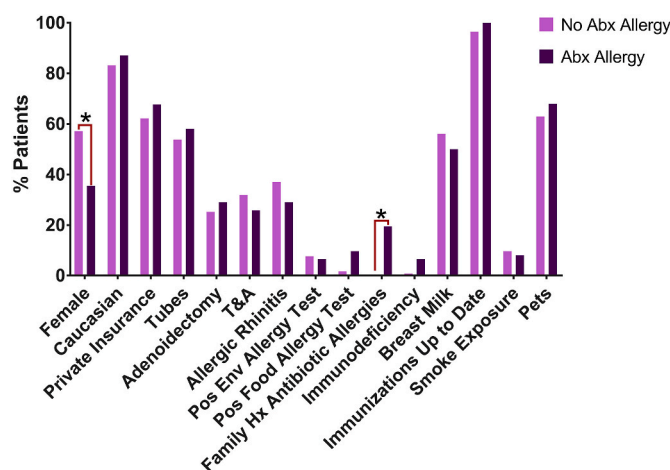


Fig. 4. Comparison of demographic characteristics and risk factors between patients with and without antibiotic allergies. *Antibiotic allergies were less common in females ($p = 0.034$) and more common in patients with a family history of antibiotic allergies ($p < 0.001$).

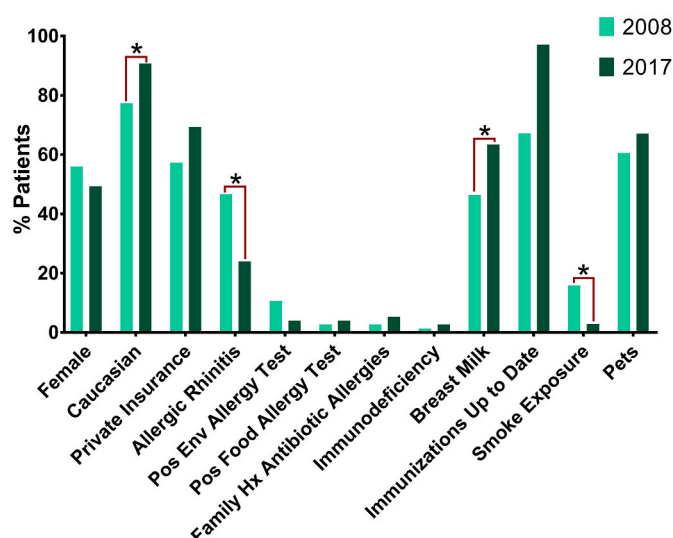


Fig. 5. Comparison of demographic characteristics and risk factors between patients with surgery in 2008 and those with surgery in 2017. *Being Caucasian ($p = 0.007$) and receiving breast milk ($p = 0.044$) were more common in 2017. Allergic rhinitis ($p = 0.004$) and smoke exposure ($p = 0.019$) were less common in 2017 than 2008.

Table 2
Multiple logistic regression for odds of antibiotic allergy.

Factor	OR	95% CI	P
All Patients			
African American	0.324	0.00702-2.55	0.498
Allergic Rhinitis	0.770	0.241-2.23	0.793
Smoke Exposure	0.904	0.0867-5.04	1.00
Surgery in 2007	1.09	0.395-3.08	1.00
Patients Receiving Tubes			
African American	1.22	0.0224-14.9	1.00
Allergic Rhinitis	1.02	0.149-5.46	1.00
Smoke Exposure	0.902	0-7.80	0.935
Surgery in 2007	2.41	0.547-13.2	0.321
Patients Undergoing Adenoidectomy Alone			
African American	0.582	0.00982-7.36	1.00
Allergic Rhinitis	1.10	0.140-9.50	1.00
Smoke Exposure	0.862	0-8.34	0.908
Surgery in 2007	0.904	0.0710-7.23	1.00
Patients Undergoing Tonsillectomy & Adenoidectomy			
African American	0.615	0-6.31	0.704
Allergic Rhinitis	0.537	0.0409-4.58	0.836
Smoke Exposure	1.20	0.0694-14.8	1.00
Surgery in 2007	0.469	0.0617-3.46	0.611

Abbreviations: CI, Confidence Interval; OR, Odds Ratio.

unable to demonstrate a difference in the prevalence of antibiotic allergies reported at our tertiary care center in 2017 compared with 2008 [17–20]. These years (2008 and 2017) corresponded to several years pre- and post-publication of guidelines in 2013, respectively [21,22]. Although not specifically examined in this study, drug allergy mislabeling, genetic predispositions to drug allergies, and inevitable exposure unaffected by antibiotic stewardship guidelines may contribute to stubbornly high prevalence of antibiotic allergies.

Antibiotics kill both pathologic and commensal bacteria. This hinders immunologic memory by reducing antigen presenting cells and IgE regulation [7,23]. Antibiotics also disrupt natural microbiota and increase novel pathogen overgrowth [24,25]. These mechanisms may underlie an increase in atopy in children who receive antibiotics early in life. For example, Mitre et al. found that children with antibiotic use in

the first 6 months of life were 2.09 times as likely to develop asthma, 1.75 times as likely to have allergic rhinitis, 1.51 times more likely to develop anaphylaxis, and 1.42 times as likely to get allergic conjunctivitis compared to children without antibiotic use [7]. In the present study, a substantial number (53, 35.3%) of patients had allergic rhinitis, 11 (7.3%) had environmental allergies, and 5 (3.3%) had food allergies.

The AAP, CDC, IDSA, and WHO emphasize narrow spectrum antibiotics, such as amoxicillin and penicillin, as first line treatment for bacterial otitis media, sinusitis, and tonsillitis, reserving broad spectrum antibiotics, such as the azalides or beta-lactam stable drugs, for severe or recurrent cases [1–3,26,27]. These organizations further published principles describing how to create and implement required antibiotic stewardship programs across hospitals. Antibiotic stewardship programs have resulted in a significant decline in antibiotic use and inappropriate use. According to national data published by the CDC, antibiotic prescriptions in children under 20 dropped from 75.2 million in 2011 to 62.5 million in 2017 [28,29]. Unfortunately, such programs have been far easier to implement and have been more successful in hospital and institutional environments whereas they have met with far less success in community-based practice which is the primary referral base for our pediatric otolaryngology surgical referrals. Although the present study did not directly examine antibiotic prescribing patterns, the difficulty in implementing stewardship programs in community-based practices could have stifled potential decreases in antibiotic prescribing and thereby precluded reductions in antibiotic allergies.

It is crucial to differentiate “allergy” from “adverse drug reactions.” Misdiagnosing adverse drug reactions as “allergic” artificially inflates the prevalence of antibiotic allergies which we believe impacted the outcome of our retrospective series. Unlike adverse reactions, antibiotic allergies are specific IgE antibody or T lymphocyte mediated immunological reactions after exposure to an antibiotic which may lead to anaphylaxis [30,31]. Diarrhea is a predictable adverse drug reaction but is not a drug allergy [32]. Rashes resulting from inappropriately prescribed antibiotics for viral etiologies may also be misdiagnosed as an IgE mediated antibiotic allergy [32]. In the United States, the prevalence of true drug allergies due to hypersensitivity is 8%, only 20% of all documented drug reactions [32]. In the present study, specific drug reactions were described for 21 out of 31 patients with reported drug allergies. Eighteen parents reported only rashes/hives, gastrointestinal complications, or swelling of the hands and feet. Only three parents reported symptoms truly consistent with an antibiotic allergy: one with throat closing; one with extreme fatigue and vomiting; and one with rashes, hives, and gastrointestinal complications. Furthermore, only one child with an antibiotic allergy underwent true allergy testing and was ironically non allergic. Viles et al. reported 67% of parents who suspect an antibiotic allergy describe symptoms inconsistent with true drug allergy [33]. Ninety-one percent of children with reported penicillin allergy were de-labeled upon proper amoxicillin testing according to Mill et al. [34]. Healthcare professionals exacerbate the problem by overriding 77–90% of charting system notifications to verify charted allergies and failing to remove or redocument 36–49% of patients deemed nonallergic after formal penicillin testing [35]. This drug allergy mislabeling could have diluted any potential difference in antibiotic allergies between the two time periods in the current study.

Genetics, immunologic predisposition, and/or concurrent illness predispose individuals to antibiotic allergies. Penicillin or beta lactam, sulfonamide, and cephalosporin allergies are most common [32]. In the present study, children with a family history of antibiotic allergies had 36-fold greater odds of having an antibiotic allergy themselves. The majority of the population studied was Caucasian and 18–30% of Europeans report confirmed penicillin allergies [36], significantly higher than the US rate of drug allergy [32]. Penicillin allergies are higher in hospitalized patients and patients receiving care for other conditions such as cancer, cystic fibrosis, and HIV/AIDs [36]. Patients with more than 3 drug allergies have a biological basis for heightened reactivity through immune modulating histamine-releasing factors, tolerances of

small chemicals, drug-induced interferon gamma release, or pre-activated CD4 T cells [31]. Genetic predisposition could have made the antibiotic allergy prevalence in the present study refractory to decreases in antibiotic exposure resulting from stewardship programs.

In our study, 20.7% of the patients were allergic to antibiotics, slightly higher than a previous estimate of 15.3% [13]. This discrepancy may be due to our specific inclusion criteria. We selected patients with a history of recurrent infection, and Li et al. demonstrated that in infancy the severity and number of infections, not antibiotic use, are independently associated with childhood obesity [37,38]. However, no studies have been done on the relationship between infection and asthma, allergic rhinitis, anaphylaxis or allergic conjunctivitis.

The limitations of our study include limited generalizability due to being conducted at a single institution. In addition, we relied on parental report for the preventative/risk factors including antibiotic allergies and drug reactions, inherent to retrospective chart review studies. The extent of antibiotic exposure prior to surgery could not be studied as we did not have access the primary care physician prescription history. The study looked at a heterogeneous group of diagnoses (otitis media, sinusitis, and tonsillitis) and surgeries (BMT and adenoidectomy with/without tonsillectomy). Although we did not find a significant difference in antibiotic allergy prevalence between surgical groups or a significant impact of patient age at surgery, we strongly suspect that the younger otitis media population is different than the older adenotonsillectomy cohort and plan to study these populations separately in the future. The more recent patients studied from 2017 may not yet reflect the impact of antibiotic stewardship which has led us to plan a study in surgical patients from 2019 to 2020. Finally, we will design future studies more appropriately powered to identify a clinically significant difference. A (non-significant) decrease in antibiotic allergies in 2017 compared with 2008 was only observed in patients undergoing tonsillectomy and adenoidectomy (22.2% vs 14.3%). With $\delta = -0.079$, power = 0.80, and $\alpha = 0.05$, a total of 750 patients (375 in each year) would be required to detect a significant change in antibiotic allergies.

These study limitations notwithstanding, we remain invested in the importance of studying antibiotic allergies specifically in a pediatric otolaryngology population. This may provide opportunities for quality improvement and modification of surgical criteria weighted towards antibiotic related outcome measures versus reductions in duration, severity, and frequency of these common and generally self-limited infections.

5. Conclusion

Pediatric otolaryngology surgical patients continue to exhibit a similar and high prevalence of antibiotic allergies in 2017 compared with 2008. Future studies are needed to determine whether this is because of overdiagnosis of antibiotic allergies or a failure of antibiotic guideline adherence to reduce antibiotic allergy prevalence.

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Declaration of competing interest

None.

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