

Association Between Use of Acid-Suppressive Medications and Antibiotics During Infancy and Allergic Diseases in Early Childhood

Edward Mitre, MD; Apryl Susi, MS; Laura E. Kropp, MPH; David J. Schwartz, MD; Gregory H. Gorman, MD; Cade M. Nylund, MD

IMPORTANCE Allergic diseases are prevalent in childhood. Early exposure to medications that can alter the microbiome, including acid-suppressive medications and antibiotics, may influence the likelihood of allergy.

OBJECTIVE To determine whether there is an association between the use of acid-suppressive medications or antibiotics in the first 6 months of infancy and development of allergic diseases in early childhood.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study was conducted in 792 130 children who were Department of Defense TRICARE beneficiaries with a birth medical record in the Military Health System database between October 1, 2001, and September 30, 2013, with continued enrollment from within 35 days of birth until at least age 1 year. Children who had an initial birth stay of greater than 7 days or were diagnosed with any of the outcome allergic conditions within the first 6 months of life were excluded from the study. Data analysis was performed from April 15, 2015, to January 4, 2018.

EXPOSURES Exposures were defined as having any dispensed prescription for a histamine-2 receptor antagonist (H_2RA), proton pump inhibitor (PPI), or antibiotic.

MAIN OUTCOMES AND MEASURES The main outcome was allergic disease, defined as the presence of food allergy, anaphylaxis, asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, urticaria, contact dermatitis, medication allergy, or other allergy.

RESULTS Of 792 130 children (395 215 [49.9%] girls) included for analysis, 60 209 (7.6%) were prescribed an H_2RA , 13 687 (1.7%) were prescribed a PPI, and 131 708 (16.6%) were prescribed an antibiotic during the first 6 months of life. Data for each child were available for a median of 4.6 years. Adjusted hazard ratios (aHRs) in children prescribed H_2RAs and PPIs, respectively, were 2.18 (95% CI, 2.04-2.33) and 2.59 (95% CI, 2.25-3.00) for food allergy, 1.70 (95% CI, 1.60-1.80) and 1.84 (95% CI, 1.56-2.17) for medication allergy, 1.51 (95% CI, 1.38-1.66) and 1.45 (95% CI, 1.22-1.73) for anaphylaxis, 1.50 (95% CI, 1.46-1.54) and 1.44 (95% CI, 1.36-1.52) for allergic rhinitis, and 1.25 (95% CI, 1.21-1.29) and 1.41 (95% CI, 1.31-1.52) for asthma. The aHRs after antibiotic prescription in the first 6 months of life were 2.09 (95% CI, 2.05-2.13) for asthma, 1.75 (95% CI, 1.72-1.78) for allergic rhinitis, 1.51 (95% CI, 1.38-1.66) for anaphylaxis, and 1.42 (95% CI, 1.34-1.50) for allergic conjunctivitis.

CONCLUSIONS AND RELEVANCE This study found associations between the use of acid-suppressive medications and antibiotics during the first 6 months of infancy and subsequent development of allergic disease. Acid-suppressive medications and antibiotics should be used during infancy only in situations of clear clinical benefit.

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 Supplemental content

Author Affiliations: Department of Microbiology and Immunology, F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland (Mitre, Kropp); Department of Pediatrics, F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland (Susi, Gorman, Nylund); Division of Allergy and Immunology, Department of Medicine, Dwight D. Eisenhower Army Medical Center, Ft Gordon, Georgia (Schwartz).

Corresponding Author: Edward Mitre, MD, Department of Microbiology and Immunology, F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd, Bethesda, MD 20814 (edward.mitre@usuhs.edu).

The cumulative prevalence of allergic diseases and asthma has risen over the past several decades. In particular, food allergy has exhibited a particularly brisk rise in children.¹⁻⁴ Furthermore, studies in the United States and other countries have demonstrated increases in allergic rhinoconjunctivitis, asthma, skin prick test positivity to common allergens, and hospitalizations due to anaphylaxis.⁵⁻⁹

An area of environmental change that may be contributing to the rise of allergic diseases is the increasing use of medications that alter the development of the human microbiome. Both gastric acid-suppressive medications and antibiotics have been implicated as factors that may enhance the development of allergic diseases.¹⁰⁻¹³ Use of these medications, which can directly cause intestinal dysbiosis, is of concern in light of increasing evidence that alterations in the human microbiome can increase the risk for allergy development.^{11,14,15} Furthermore, acid-suppressive medications, which reduce protein digestion, can affect how ingested antigens are processed in the intestinal tract. Acid suppression has been shown to increase immunoglobulin (Ig) E production in response to orally ingested antigens in animal studies^{16,17} and has been associated with food and medication allergy in humans.¹⁸⁻²⁰

The objective of this study was to evaluate the hypothesis that exposure to either acid-suppressive medications or antibiotics during infancy is associated with an increased risk of childhood allergic diseases. We tested this hypothesis by conducting a retrospective cohort analysis investigating the development of allergy in children in the TRICARE Management Activity Military Health System (MHS) database.

Methods

Data Source and Inclusion Criteria

A retrospective cohort study was performed using the TRICARE Management Activity MHS database. TRICARE Management Activity oversees health care delivery for US uniformed service members and their dependents. The MHS database includes all outpatient and inpatient billing records as well as outpatient pharmacy use for all eligible uniformed services members and their dependents in both military and civilian facilities. The database includes billing data for military patients seen outside the direct care military system. The MHS database was queried to identify all children eligible for health care starting at birth. To be included in the study, children must have had a birth medical record in the database between October 1, 2001, and September 30, 2013, and continued enrollment from within 35 days of birth until at least age 1 year. Also, children who were diagnosed with any of the outcome allergic conditions within the first 6 months of life were excluded from the study, as were children who had incomplete enrollment or demographic data and children who had an initial birth stay of greater than 7 days (Figure 1).

The study was reviewed and approved by the institutional review board of the Uniformed Services University with waiver of informed consent. Data were deidentified.

Key Points

Question Does use of medications that disturb the microbiome in infancy increase subsequent risk of developing allergic diseases?

Findings In this cohort study of 792 130 children, the hazard of developing an allergic disease was significantly increased in those who had received acid-suppressive medications or antibiotics during the first 6 months of life.

Meaning Exposure to acid-suppressive medications or antibiotics in the first 6 months of life may increase risk of allergic disease development.

Variable Definitions

The MHS database was used to identify children prescribed an outpatient histamine-2 receptor antagonist (H₂RA), proton pump inhibitor (PPI), or antibiotic at any time prior to age 6 months using the American Hospital Formulary Service classification (listed in eTable 1 in the [Supplement](#)).²¹ The name of the medication, the number of days supplied, and the age at which the prescription was dispensed were extracted for each eligible child. Exposures for the primary analysis were defined as binary time-fixed variables, categorically defined as any dispensed H₂RA, PPI, or antibiotic in the first 6 months of life.

Allergic disease outcomes were defined using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnostic codes. For each child, the outcomes were evaluated from age 6 months and censored at time of health care disenrollment or the end of the study (September 30, 2014). Each child's outpatient and inpatient medical visits were extracted using MHS claim files from October 1, 2001, to September 30, 2014. An event was defined as the first medical encounter with the specific allergic condition categorized by ICD-9-CM diagnostic codes listed in eTable 2 in the [Supplement](#). Additional variables obtained using ICD-9-CM codes included prematurity and birth by cesarean delivery (eTable 2 in the [Supplement](#)).

Statistical Analysis

We summarized continuous data with medians and interquartile ranges (IQRs) and categorical data with numbers and percentages. Because the medication groups were not mutually exclusive, comparison of demographics and other variables for children receiving H₂RAs, PPIs, antibiotics, or no medications were compared using repeated-measures methods.²² Cox proportional hazards regression was used to calculate the hazard ratio (HR) of developing an allergic condition based on exposure to PPIs, H₂RAs, and antibiotics in the first 6 months of life. In the adjusted models, adjusted HRs (aHRs) were calculated after adjusting for prematurity, cesarean delivery, sex, the other drug classes, and any significant first-order interaction terms. The Cox proportional hazards regression assumption was evaluated by visual inspection for parallelism of the log-log survival curves for each variable in the models as well as evaluating correlation

of the Schoenfeld residuals with time. When variables violated the Cox proportional hazards regression assumption with either log-log curves that were not parallel or the Schoenfeld residuals with time were significant, an interaction of the variable with time was included in the model.²³

For evaluating whether there is a dose-related risk of developing allergy, patient groups receiving H₂RAs or PPIs were divided into those receiving no medication, 1 to 60 days of medication, and more than 60 days of medication. For antibiotic use, low and high doses were defined as up to and including 10 days and over 10 days of antibiotics. Cutoff levels for low and high doses of acid-suppressive medications and antibiotics were based on median days prescribed. Cox proportional hazards regression was used to evaluate the HR for these medication groups. Estimated survival curves based on the Cox proportional hazards regression models were constructed for visualization purposes.²⁴ In addition, a subanalysis was performed to evaluate the effect of medications among those who had a diagnosis of gastroesophageal reflux disease (GERD). Data analysis was conducted from April 15, 2015, to January 4, 2018.

Two-tailed *P* values <.05 were considered statistically significant. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

Results

Patient Characteristics and Use of Acid-Suppressive Medications and Antibiotics

A total of 792 130 children had birth medical records in the database between October 1, 2001, and September 30, 2013, and met all other inclusion criteria (Figure 1). During the first 6 months of life, 60 209 children (7.6%) were prescribed an H₂RA, 13 687 (1.7%) were prescribed a PPI, and 131 708 (16.6%) were prescribed an antibiotic (Table 1). Several children were prescribed multiple medications. Of all children, 12 546 (1.6%) received H₂RAs and antibiotics, 5520 (0.7%) received H₂RAs and PPIs, 1590 (0.2%) received PPIs and antibiotics, and 2549 (0.3%) received all 3 medications. Data for each child were available for a median of 4.6 years (IQR, 2.5-7.9).

The most frequently used H₂RA was ranitidine, accounting for 95.1% of all H₂RA prescriptions. The next most frequently prescribed H₂RAs were nizatidine and famotidine. Lansoprazole was the most commonly prescribed PPI, totaling 75.5% of all days supplied of PPI prescriptions. The median days supplied for both H₂RAs and PPIs was 60 (IQR for H₂RAs, 39-92; IQR for PPIs, 30-91).

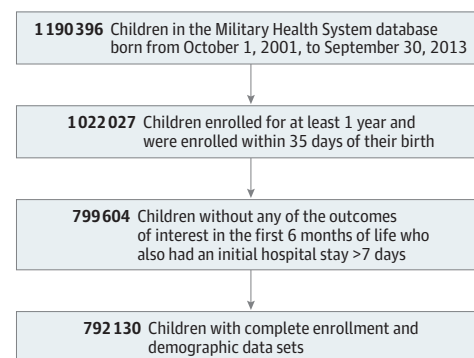
Median days of antibiotics prescribed was 10 (IQR, 10-20), and the total number of days was more than 3.4 million. The most common classes were penicillins, comprising 65.3% of the total days of prescribed antibiotics, cephalosporins comprising 14.2%, and macrolides comprising 10.1%. The top 3 individual antibiotics prescribed were amoxicillin (55.0%), amoxicillin clavulanate (9.0%), and trimethoprim with sulfamethoxazole (8.7%). Among those prescribed antibiotics in the first 6 months of life, the median age at which children were first prescribed antibiotics was 125 days (IQR, 88-155) and was greater than the age of first prescription for both H₂RAs (61 days: IQR, 37-94) and PPIs (73 days: IQR, 47-117).

A greater percentage of boys was prescribed H₂RAs (32 052 [8.1%]), PPIs (7491 [1.9%]), and antibiotics (70 933 [17.9%]) than girls (28 157 [7.1%] for H₂RAs; 6196 [1.6%] for PPIs; and 60 775 [15.4%] for antibiotics; *P* < .001 for all comparisons). Premature infants were more likely to be prescribed H₂RAs (4177 [13.4%]) and PPIs (1040 [3.3%]) than full-term infants (56 032 [7.4%] for H₂RAs; 12 647 [1.7%] for PPIs; *P* < .001 for both comparisons). There was no significant difference in the percentage of children born prematurely given antibiotics compared with full-term infants (5212 [16.8%] vs 126 496 [16.1%]; *P* = .46).

Allergy Diagnoses

Of the 792 130 children in this cohort, 24 514 (58.7/10 000 person-years) were diagnosed with a food allergy. Among the identified food allergies, peanut allergy was the most

Figure 1. Patient Selection



Patients were selected on the basis of having a birth medical record in the Military Health System database between October 1, 2001, and September 30, 2013, with continued enrollment from within 35 days of birth until at least age 1 year. Exclusion criteria included initial birth stay of greater than 7 days, diagnosis of any of the outcome allergic conditions within the first 6 months of life, and incomplete enrollment and demographic data sets.

Table 1. Baseline Patient Characteristics and Medication Use

Characteristic	No. (%)				
	Population (N = 792 130)	No Medications (n = 611 370)	Antibiotics (n = 131 708)	H ₂ RAs (n = 60 209)	PPIs (n = 13 687)
Girls	395 215 (49.9)	311 086 (50.9)	60 775 (46.1)	28 157 (46.8)	6196 (45.3)
Boys	396 915 (50.1)	300 284 (49.1)	70 933 (53.9)	32 052 (53.2)	7491 (54.7)
Cesarean delivery	206 637 (26.1)	155 564 (25.4)	36 125 (27.4)	18 360 (30.5)	4351 (31.8)
Prematurity	31 061 (3.9)	22 378 (3.7)	5212 (4.0)	4177 (6.9)	1040 (7.6)

Abbreviations: H₂RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors.

Table 2. Incidence of Allergic Diseases in Children Given Antibiotics, H₂RAs, or PPIs During Infancy^a

Characteristic	Age at First Diagnosis, Median (IQR), y ^b	Total Population		No Drug Exposure		Antibiotics		H ₂ RAs		PPIs	
		No. (% of 792 130)	Incidence Density	No. (% of 611 370)	Incidence Density	No. (% of 131 708)	Incidence Density	No. (% of 60 209)	Incidence Density	No. (% of 13 687)	Incidence Density
Any food allergy	2.1 (1.2-4.2)	24 514 (3.1)	58.7	17 401 (2.8)	53.5	4753 (3.6)	66.6	2918 (4.8)	113.8	834 (6.1)	142.9
Cow's milk	1.4 (1.0-2.7)	4544 (0.6)	10.7	2930 (0.5)	8.9	985 (0.7)	13.6	793 (1.3)	30.2	283 (2.1)	47.2
Peanut	2.6 (1.5-4.1)	5833 (0.7)	13.8	4368 (0.7)	13.2	1070 (0.8)	14.7	477 (0.8)	18.1	127 (0.9)	20.9
Egg	1.8 (1.2-3.3)	3038 (0.4)	7.2	2139 (0.3)	6.5	610 (0.5)	8.4	342 (0.6)	12.9	87 (0.6)	14.3
Seafood	4.4 (2.6-6.5)	1157 (0.1)	2.7	872 (0.1)	2.6	213 (0.2)	2.9	86 (0.1)	3.2	22 (0.2)	3.6
Other food	2.5 (1.3-4.8)	17 559 (2.2)	41.8	12 522 (2.0)	38.3	3358 (2.5)	46.7	2078 (3.5)	80.1	594 (4.3)	100.2
Anaphylaxis	3.0 (1.6-5.2)	5705 (0.7)	13.5	4124 (0.7)	12.5	1139 (0.9)	15.7	562 (0.9)	21.3	147 (1.1)	24.3
Asthma	2.0 (1.1-3.7)	111 792 (14.1)	297.7	77 327 (12.6)	261.0	27 488 (20.9)	456.0	9818 (16.3)	428.3	2568 (18.8)	494.8
Atopic dermatitis	1.5 (0.9-3.0)	112 608 (14.2)	300.0	83 978 (13.7)	286.4	21 638 (16.4)	342.5	8887 (14.8)	380.6	2165 (15.8)	406.1
Allergic rhinitis	2.3 (1.3-4.2)	248 232 (31.3)	771.5	180 224 (29.5)	705.4	52 135 (39.6)	1038.8	20 926 (34.8)	1080.8	5134 (37.5)	1168.3
Allergic conjunctivitis	4.2 (2.2-6.5)	24 585 (3.1)	59.0	18 141 (3.0)	55.9	5047 (3.8)	71.0	1793 (3.0)	69.1	436 (3.2)	73.1
Urticaria	2.2 (1.3-4.0)	71 547 (9.0)	180.4	53 767 (8.8)	173.9	13 137 (10.0)	194.5	5836 (9.7)	237.1	1391 (10.2)	245.9
Other allergy	2.8 (1.4-5.0)	65 887 (8.3)	164.4	48 083 (7.9)	153.6	13 229 (10.0)	194.9	5791 (9.6)	234.6	1385 (10.1)	244.3
Contact dermatitis	1.5 (0.9-2.9)	230 990 (29.2)	703.2	173 176 (28.3)	671.9	43 035 (32.7)	791.4	18 570 (30.8)	922.3	4438 (32.4)	966.9
Medication allergy	2.6 (1.4-5.0)	12 925 (1.6)	30.7	8964 (1.5)	27.3	2883 (2.2)	40.0	1436 (2.4)	55.0	393 (2.9)	65.6

Abbreviations: H₂RAs, histamine-2 receptor antagonists; IQR, interquartile range; PPIs, proton pump inhibitors.

^a Incidence densities defined as cases per 10 000 person-years.

^b Infants diagnosed with any of the outcome allergic conditions within the first 6 months of life were excluded from the study cohort.

common (13.8/10 000 person-years), followed by cow's milk allergy (10.7/10,000 person-years) and egg allergy (7.2/10 000 person-years) (Table 2).

With regard to other allergic diseases, the 2 most common diagnoses were allergic rhinitis (771.5/10 000 person-years) and contact dermatitis (703.2/10 000 person-years). The next most common nonfood allergies were atopic dermatitis (300.0/10 000 person-years), asthma (297.7/10 000 person-years), and urticaria (180.4/10 000 person-years) (Table 2).

All covariates analyzed exhibited a statistically significant association with allergic disease (eTable 3 in the Supplement). A greater percentage of boys developed an allergic condition than girls (59.5% vs 56.6%; $P < .001$). Children born by cesarean delivery and those born prematurely also demonstrated an increased risk of allergic disease compared with children without those conditions (59.4% vs 57.5% and 59.0% vs 58.0%, respectively; $P < .001$ for both).

Association Between Acid-Suppressive Medications and Allergic Diseases

Every allergic disease assessed exhibited a significantly increased risk in children who had received H₂RAs or PPIs

during infancy except for seafood allergy (Table 3), which had the lowest incidence of the conditions evaluated (Table 2). Adjusted HRs were greatest for food allergies as a category, with an aHR of 2.18 for H₂RAs (95% CI, 2.04-2.33) and an aHR of 2.59 (95% CI, 2.25-3.00) for PPIs. Of the specific types of food allergies, use of acid-suppressive medications increased the risk of being diagnosed with cow's milk allergy the most (aHR, 2.42; 95% CI, 2.22-2.64 for H₂RAs and aHR, 4.43; 95% CI, 3.48-5.65 for PPIs). For children who received H₂RAs, the aHRs for developing peanut, egg, or other food allergies were 1.21 (95% CI, 1.09-1.33), 1.74 (95% CI, 1.52-1.99), and 2.13 (95% CI, 1.98-2.30), respectively. Similarly, prescription of PPIs during infancy was associated with an aHR for peanut, egg, or other food allergies of 1.27 (95% CI, 1.05-1.52), 1.35 (95% CI, 1.08-1.69), and 2.68 (95% CI, 2.23-3.20), respectively. Consistent with the entire study population, children diagnosed with GERD during infancy also demonstrated increased incidence densities and aHRs for food allergy after treatment with H₂RAs and PPIs (eTables 4 and 5 in the Supplement).

Risk of food allergy after treatment with acid-suppressive medications exhibited a dose-dependent effect with regard to days of medication prescribed (antibiotic short dura-

Table 3. aHRs for Allergic Diseases in Children Given Antibiotics, H₂RAs, or PPIs During Infancy

Characteristic	aHR (95% CI)		
	Antibiotics	H ₂ RAs	PPIs
Any food allergy	1.14 (1.10-1.18)	2.18 (2.04-2.33)	2.59 (2.25-3.00)
Cow's milk	1.24 (1.15-1.33)	2.42 (2.22-2.64)	4.43 (3.48-5.65)
Peanut	1.06 (0.99-1.14)	1.21 (1.09-1.33)	1.27 (1.05-1.52)
Egg	1.24 (1.13-1.37)	1.74 (1.52-1.99)	1.35 (1.08-1.69)
Seafood	1.05 (0.91-1.22)	1.24 (0.98-1.56)	1.24 (0.80-1.94)
Other food	1.11 (1.06-1.15)	2.13 (1.98-2.30)	2.68 (2.23-3.20)
Anaphylaxis	1.51 (1.38-1.66)	1.51 (1.38-1.66)	1.45 (1.22-1.73)
Asthma	2.09 (2.05-2.13)	1.25 (1.21-1.29)	1.41 (1.31-1.52)
Atopic dermatitis	1.18 (1.16-1.19)	1.12 (1.09-1.14)	1.12 (1.07-1.17)
Allergic rhinitis	1.75 (1.72-1.78)	1.50 (1.46-1.54)	1.44 (1.36-1.52)
Allergic conjunctivitis	1.42 (1.34-1.50)	1.48 (1.35-1.62)	1.15 (1.04-1.27)
Urticaria	1.09 (1.07-1.11)	1.30 (1.24-1.35)	1.27 (1.17-1.38)
Other allergy	1.30 (1.26-1.34)	1.63 (1.55-1.71)	1.62 (1.45-1.80)
Contact dermatitis	1.16 (1.14-1.19)	1.25 (1.22-1.28)	1.21 (1.15-1.28)
Medication allergy	1.34 (1.29-1.40)	1.70 (1.60-1.80)	1.84 (1.56-2.17)

Abbreviations: aHRs, adjusted hazard ratio; H₂RAs, histamine-2 receptor antagonists; PPIs, proton pump inhibitors.

tion indicates 10 or fewer days; long duration, 11 or more days; H₂RA and PPI short duration, 60 or fewer days; long duration, 61 or more days) (Figure 2). Children prescribed more than 60 days of PPIs had a 52% greater risk of being diagnosed with food allergy during childhood than those prescribed 1 to 60 days of PPIs (aHR of food allergy in children prescribed >60 days vs 1-60 days of PPIs: 1.52; 95% CI, 1.32-1.74). A dose-dependent effect was also observed with H₂RAs (aHR of food allergy in children prescribed >60 days of H₂RA vs 1-60 days: 1.32; 95% CI, 1.23-1.43).

All nonfood allergic diseases studies also were found to be significantly associated with the use of acid-suppressive medication therapy during infancy (Table 3). Of the nonfood allergy-related conditions, the allergic diseases exhibiting the greatest increased risk after acid-suppressive therapy were medication allergy (aHR, 1.70; 95% CI, 1.60-1.80 for H₂RAs and 1.84; 95% CI, 1.56-2.17 for PPIs), allergic rhinitis (aHR, 1.50; 95% CI, 1.46-1.54 for H₂RAs and 1.44; 95% CI, 1.36-1.52 for PPIs), anaphylaxis (aHR, 1.51; 95% CI, 1.38-1.66 for H₂RAs and 1.45; 95% CI, 1.22-1.73 for PPIs), and other allergy (aHR, 1.63; 95% CI, 1.55-1.71 for H₂RAs and 1.62; 95% CI, 1.45-1.80 for PPIs). Acid-suppressive medication therapy was also associated with a marked increase in asthma, allergic conjunctivitis, and urticaria during childhood.

Association Between Antibiotics and Allergic Diseases

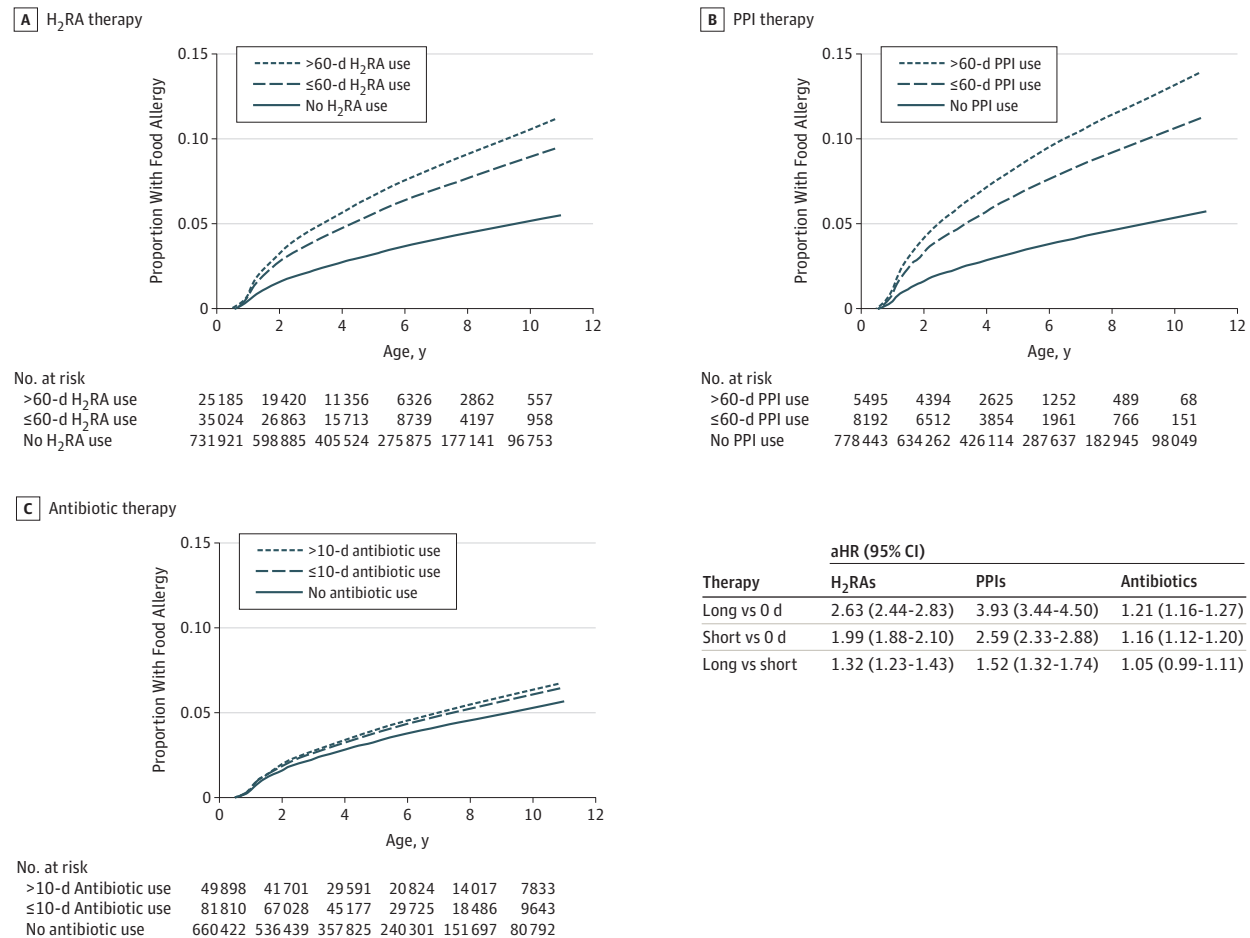
As with acid-suppressive medications, prescriptions for antibiotics during infancy also were significantly associated with an increased risk of allergic diseases. The aHR for development of any food allergy was 1.14 (95% CI, 1.10-1.18) in children who had received antibiotics. While neither peanut allergy nor seafood allergy exhibited significantly increased risk, antibiotic use during infancy was associated with an increased risk of both cow's milk allergy and egg allergy (aHR, 1.24 for both; 95% CI, 1.15-1.33 for cow's milk allergy and 95% CI, 1.13-1.37 for egg allergy). Unlike acid-suppressive medications, antibiotics did not demonstrate a dose-dependent risk

for development of food allergy (aHR, 1.05; 95% CI, 0.99-1.11 for developing any food allergy in children prescribed >10 days of antibiotics compared with children prescribed 1-10 days) (Figure 2C).

Several nonfood allergic diseases were significantly increased in children who had received antibiotics during infancy. Antibiotics prescribed during infancy were associated with a greater than 2-fold risk of asthma in childhood (aHR, 2.09; 95% CI, 2.05-2.13). Risks of anaphylaxis (aHR, 1.51; 95% CI, 1.38-1.66), allergic conjunctivitis (aHR, 1.42; 95% CI, 1.34-1.50), and medication allergy (aHR, 1.34; 95% CI, 1.29-1.40) also were significantly increased in children who had received antibiotics as infants (Table 3). In addition, the incidence of atopic dermatitis, allergic rhinitis, contact dermatitis, urticaria, and other allergies were significantly increased in children who were prescribed antibiotics during infancy (Table 3).

Discussion

In this retrospective cohort study of 792 130 children, we found significant associations between the use of acid-suppressive medications or antibiotics in infancy and the development of allergic diseases in childhood. Use of acid-suppressive medications was positively associated with increased risks for all major categories of allergic disease and most strongly associated with food allergy. Infants prescribed H₂RAs and PPIs during the first 6 months of infancy exhibited respective aHRs for food allergy of 2.18 and 2.59. Antibiotics were also significantly associated with all major categories of allergic disease. The aHRs after antibiotic prescription in the first 6 months of life were 2.09 for asthma, 1.14 for food allergy, and 1.40 or greater for anaphylaxis, allergic rhinitis, and allergic conjunctivitis. This study adds to the mounting evidence that agents that disrupt the normal intestinal microbiome during infancy may increase the development of allergic diseases.

Figure 2. Incidence of Food Allergy and Duration of Histamine-2 Receptor Antagonist (H₂RA), Proton Pump Inhibitor (PPI), and Antibiotic Prescribed During the First 6 Months of Life

Incidence for H₂RA (A), PPI (B), and antibiotic (C) therapy prescribed. Inset table reports adjusted hazard ratios (aHRs) for development of food allergy

determined by duration of medicine prescribed. Duration is defined in Results section.

With respect to acid-suppressive medications, both adults and children have been shown to have a greater risk of food allergy after a course of acid-suppressive therapy.^{18,20} Acid-suppressive medications may enhance allergic responses not only to food allergens but also to nonfood allergens. In our study, all of the nonfood allergies examined were significantly increased in children who had received H₂RAs or PPIs during infancy. Our results are consistent with those of a murine study that observed increased levels of allergen-specific IgE following intraperitoneal sensitization with cimetidine,²⁵ as well as with a human study in Spain that found that use of PPIs during hospitalization is associated with increased risks of allergy to injected and orally administered medications.¹⁹

Our results are also in line with those of prior investigations that suggest a link between administration of antibiotics early in life and subsequent development of allergic diseases. A systematic review published in 2011 found that children given antibiotics in the first year of life had a pooled odds ratio of 1.52 for risk of allergy.²⁶ Similarly, a recent retrospective study of 30 060 children in the United States found

strong associations between antibiotic use in the first 3 months of life and subsequent development of food and nonfood allergic diseases.²⁷ In our study, food allergy, atopic dermatitis, urticaria, contact dermatitis, medication allergy, allergic conjunctivitis, and anaphylaxis were increased by 9% to 51% in children who had been prescribed antibiotics during the first 6 months of life. Antibiotics were associated with an even greater risk for development of allergic diseases triggered by aeroallergens. Asthma was increased by over 100% and allergic rhinitis by 75% in children exposed to antibiotics during infancy.

While not fully understood, potential mechanisms by which acid-suppressive medications and antibiotics can increase allergic sensitization include intestinal dysbiosis and, for acid-suppressive medications, decreased protein digestion in the stomach.¹³ There is mounting evidence from human and animal studies that a diverse microbiome plays a central role in the development of a healthy immune system and that perturbations in the microbiome can increase the risk for allergic diseases.^{11,14,15,28,29} Studies suggest that healthy nor-

mal flora modulate innate immune responses and augment regulatory T-cell populations, potentially by production of short-chain fatty acids.²⁸ The status of the microbiome early in life appears to be especially important, as animal studies have shown that antibiotic treatment of neonatal mice—but not adult mice—increases the risk of allergic disease.^{30,31}

Acid-suppressive medications were associated with a greater risk of food allergy than antibiotic use. In addition to causing intestinal dysbiosis, acid-suppressive medications may increase sensitization to ingested antigens by decreasing protein breakdown in the stomach. Animal studies have shown that acid suppression inhibits the breakdown of ingested proteins and facilitates IgE antibody production.^{16,17} In addition, H₂RAs may increase the risk of allergic disease by direct effects on the immune system as histamine is increasingly recognized as having a role in modulating immune system function.³²

While there has been increasing recognition of the potential risks of antibiotic use during infancy, H₂RAs and PPIs are considered to be generally safe and are commonly prescribed for children younger than 1 year.^{33,34} In the present study, 7.6% of all infants were prescribed an H₂RA and 1.7% were prescribed a PPI. These medications are frequently given to infants who regurgitate food and appear to be fussy. For most infants, however, regurgitation of gastric contents is not a disease, but rather is a developmentally normal process.³⁵ A systematic review found little evidence to support the efficacy of H₂RAs in infants,³⁶ and trials have not found clinical benefit of PPI therapy in infants with symptoms attributed to gastroesophageal reflux.^{37,38} Accordingly, commentaries have advised against the overuse of acid-suppressive medications in infants.^{35,39}

Limitations

A limitation of this study is the potential bias from reverse causality because it is possible that acid-suppressive medications

or antibiotics were given for allergic diseases that were misdiagnosed as GERD or infectious diseases. While this bias may have played a role, it is unlikely to explain the entirety of our findings. The increased rates of anaphylaxis, urticaria, and medication allergy observed in this study are not likely due to reverse causality because their clinical manifestations do not substantially overlap with GERD or infectious diseases. With regard to food allergy, which can be confused with GERD in infants,⁴⁰ the rates of this disease in children younger than 6 months may be too low to have been the main driver of acid-suppressive medication prescriptions in this study. A birth cohort study that confirmed cases by the use of a double-blind, placebo-controlled food challenge found an adjusted incidence of cow's milk allergy of only 0.54% during the first 2 years of life.⁴¹ In addition, in our subanalysis among those with a diagnosis of GERD, we found statistically significant increases in food allergy for infants prescribed H₂RAs and PPIs. This finding suggests that the identified association for these medications is likely not driven exclusively by misclassified cases of food allergies manifesting with symptoms of GERD.

Conclusions

To our knowledge, this is the largest study demonstrating an association between H₂RAs, PPIs, and antibiotics given during infancy and the subsequent development of allergic diseases. The results are consistent with those of prior studies and have biological plausibility. Thus, this study provides further impetus that antibiotics and acid-suppressive medications should be used during infancy only in situations of clear clinical benefit. Additional studies will be required to confirm causality and determine the mechanism of action.

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Study concept and design: Mitre, Susi, Gorman, Nylund.

Acquisition, analysis, or interpretation of data: All authors.

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08.12.20 sulfonamides

08.12.24 tetracyclines

08.12.28 miscellaneous antibiotics (including clindamycin)

08.14.08 azoles

(additionally, specific searches performed in the drug name field for linezolid, colistmethate sodium, and metronidazole)

Proton pump inhibitors: 56.28.36 (omeprazole, lansoprazole, esomeprazole, pantoprazole, dexlansoprazole, and rabeprazole)

H2 Receptor antagonists: 56.28.12 (cimetidine, famotidine, nizatidine, and ranitidine)

eTable2. *International Classification of Diseases, 9th revision, Clinical Modification*
Diagnostic Codes Used in Study

Peanut allergy	V1501
Milk allergy	V1502
Egg allergy	V1503
Seafood allergy	V1504
Other food allergy	V1505, 9957
Anaphylaxis	9956, 99560, 99561, 99562, 99563, 99564, 99565, 99566, 99567, 99568, 99569, 9950
Asthma	4930, 49300, 49301, 49302, 4931, 49310, 49311, 49312, 4932, 49320, 49321, 49322, 4938, 49381, 49382, 4939, 49390, 49391, 49392
Atopic Dermatitis	6918, 6920, 6921, 6922, 6923, 6925, 6926, 6928, 69281, 69283,
Allergic Rhinitis	477, 4770, 4772, 4778, 4779
Allergic Conjunctivitis	37205, 37214
Urticaria	708, 7080, 7081, 7082, 7083, 7084, 7085, 7088, 7089
Other Allergy	V1507, V1509, 9994, 99941, 99949, 99527, 9953
Contact Dermatitis	6924, 69284, 69289, 6929, 6930, 6931, 6938, 6939,
Medication Allergy	V140, V141, V142, V143, V144, V145, V146, V147, V148, V149
Prematurity	76521, 76522, 76523, 76524, 76525, 76526, 76527, 76528
Cesarean section	V3001, V3101, V3201, V3301, V3401, V3501, V3601, V3701, V3901, 7634

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	Male vs Female Adjusted Hazard Ratio (95% CI)	Cesarean Section Adjusted Hazard Ratio (95% CI)	Prematurity Adjusted Hazard Ratio (95% CI)
Any Food Allergy	1.13 (1.11-1.18)	1.07 (1.05-1.11)	1.04 (0.98-1.11)
Cow's Milk Allergy	1.24 (1.14-1.29)	1.1 (1.04-1.19)	1.12 (0.98-1.29)
Peanut Allergy	1.28 (1.22-1.35)	1.06 (1.004-1.13)	1.02 (0.89-1.16)
Egg Allergy	1.18 (1.08-1.28)	1.27 (1.14-1.40)	1.25 (1.004-1.55)
Seafood Allergy	1.20 (1.07-1.28)	1.20 (1.05-1.36)	1.18 (0.89-1.55)
Other Food Allergy	1.13 (1.09-1.16)	1.06 (1.02-1.09)	1.05 (0.97-1.13)
Anaphylaxis	1.31 (1.24-1.38)	1.06 (1.001-1.13)	1.03 (0.90-1.18)
Asthma	1.55 (1.53-1.58)	1.10 (1.09-1.12)	1.44 (1.39-1.50)
Atopic Dermatitis	1.10 (1.08-1.12)	1.06 (1.04-1.07)	0.98 (0.95-1.01)
Allergic Rhinitis	1.12 (1.11-1.13)	1.11 (1.10-1.13)	1.06 (1.03-1.09)
Allergic Conjunctivitis	1.24 (1.21-1.27)	1.09 (1.06-1.12)	1.09 (1.02-1.16)
Urticaria	1.03 (1.01-1.04)	1.03 (1.01-1.05)	0.98 (0.94-1.01)
Other Allergy	1.11 (1.10-1.13)	1.07 (1.05-1.09)	0.98 (0.93-1.03)
Contact Dermatitis	1.07 (1.06-1.08)	1.03 (1.02-1.04)	1.01 (0.98-1.03)
Medication Allergy	1.17 (1.11-1.23)	1.10 (1.06-1.14)	1.10 (1.02-1.20)

eTable 4. Incidence Densities (in Cases per 10,000 Person-Years) of Food and Non-Food Allergic Diseases In Children Diagnosed With GERD During Infancy and Given Antibiotics, H2RAs, or PPIs Prior to 6 Months of Age.

	<i>No Drug Exposure (n=33,634)</i>	<i>Antibiotics (n=22,626)</i>	<i>H2RA (n=49,681)</i>	<i>PPI (n=12,128)</i>
Any Food Allergy	73.8	101.3	118.8	153.0
Any Non-Food Allergy	2424.9	3322.5	2834.7	3006.3

eTable 5. Adjusted Hazard Ratios for Food and Non-Food Allergic Diseases in Children Diagnosed With GERD During Infancy and Given Antibiotics, H2RAs, or PPIs Prior to 6 Months of Age.

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Any Food Allergy	1.02 (0.95-1.09)	1.50 (1.38-1.64)	1.93 (1.73-2.16)
Any Non-Food Allergy	1.44 (1.39-1.49)	1.07 (1.03-1.10)	1.16 (1.10-1.21)

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Other Food Allergy	1.13 (1.09-1.16)	1.06 (1.02-1.09)	1.05 (0.97-1.13)
Anaphylaxis	1.31 (1.24-1.38)	1.06 (1.001-1.13)	1.03 (0.90-1.18)
Asthma	1.55 (1.53-1.58)	1.10 (1.09-1.12)	1.44 (1.39-1.50)
Atopic Dermatitis	1.10 (1.08-1.12)	1.06 (1.04-1.07)	0.98 (0.95-1.01)
Allergic Rhinitis	1.12 (1.11-1.13)	1.11 (1.10-1.13)	1.06 (1.03-1.09)
Allergic Conjunctivitis	1.24 (1.21-1.27)	1.09 (1.06-1.12)	1.09 (1.02-1.16)
Urticaria	1.03 (1.01-1.04)	1.03 (1.01-1.05)	0.98 (0.94-1.01)
Other Allergy	1.11 (1.10-1.13)	1.07 (1.05-1.09)	0.98 (0.93-1.03)
Contact Dermatitis	1.07 (1.06-1.08)	1.03 (1.02-1.04)	1.01 (0.98-1.03)
Medication Allergy	1.17 (1.11-1.23)	1.10 (1.06-1.14)	1.10 (1.02-1.20)

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Any Non-Food Allergy	1.44 (1.39-1.49)	1.07 (1.03-1.10)	1.16 (1.10-1.21)

Supplementary Online Content

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(additionally, specific searches performed in the drug name field for linezolid, colistmethate sodium, and metronidazole)

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Egg allergy	V1503
Seafood allergy	V1504
Other food allergy	V1505, 9957
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Asthma	4930, 49300, 49301, 49302, 4931, 49310, 49311, 49312, 4932, 49320, 49321, 49322, 4938, 49381, 49382, 4939, 49390, 49391, 49392
Atopic Dermatitis	6918, 6920, 6921, 6922, 6923, 6925, 6926, 6928, 69281, 69283,
Allergic Rhinitis	477, 4770, 4772, 4778, 4779
Allergic Conjunctivitis	37205, 37214
Urticaria	708, 7080, 7081, 7082, 7083, 7084, 7085, 7088, 7089
Other Allergy	V1507, V1509, 9994, 99941, 99949, 99527, 9953
Contact Dermatitis	6924, 69284, 69289, 6929, 6930, 6931, 6938, 6939,
Medication Allergy	V140, V141, V142, V143, V144, V145, V146, V147, V148, V149
Prematurity	76521, 76522, 76523, 76524, 76525, 76526, 76527, 76528
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	Male vs Female Adjusted Hazard Ratio (95% CI)	Cesarean Section Adjusted Hazard Ratio (95% CI)	Prematurity Adjusted Hazard Ratio (95% CI)
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Seafood Allergy	1.20 (1.07-1.28)	1.20 (1.05-1.36)	1.18 (0.89-1.55)
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Asthma	1.55 (1.53-1.58)	1.10 (1.09-1.12)	1.44 (1.39-1.50)
Atopic Dermatitis	1.10 (1.08-1.12)	1.06 (1.04-1.07)	0.98 (0.95-1.01)
Allergic Rhinitis	1.12 (1.11-1.13)	1.11 (1.10-1.13)	1.06 (1.03-1.09)
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Urticaria	1.03 (1.01-1.04)	1.03 (1.01-1.05)	0.98 (0.94-1.01)
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Letters

COMMENT & RESPONSE

Antibiotics and Acid-Suppressing Medications in Early Life and Allergic Disorders

To the Editor We thank Mitre et al¹ for their work retrospectively identifying an association between early exposure to acid-suppressive medications and subsequent development of allergic diseases in early childhood.¹ While the authors readily acknowledge the limitation of potential reverse causality, we hypothesize this may account substantially for their observed association between acid suppression and food allergy, despite efforts to address it.

The reported association was strongest between acid suppression and milk allergy, but in fact, many infants who are prescribed acid-suppressive medications in infancy already have one of several forms of early (immunoglobulin E [IgE]- or non-IgE-mediated) food allergy, of which milk is the most common. Allergic proctocolitis (AP) is a non-IgE-mediated reaction (commonly to milk) typically diagnosed in the first few months of life, presenting with symptoms of reflux, fussiness, and blood (often microscopic) in the stool that resolves with dietary restriction. The authors state that the incidence of “food allergy confused with GERD [gastroesophageal reflux disease]”¹ would be too low to affect their results; however, in our ongoing prospective healthy infant cohort study designed to study infants with allergic proctocolitis over 3 years, the cumulative incidence is 16%.² While the authors excluded children who received a diagnosis of having any of the outcome allergic conditions, they did not exclude those with several diagnoses often given to children with AP (allergic colitis or cow’s milk protein intolerance).

This also affects the subgroup analysis of infants with GERD because infants who receive a diagnosis having GERD in infancy largely receive their diagnosis based on symptoms that overlap significantly with AP. It is our strong clinical impression that many children with AP are currently prescribed acid

suppression, while current guidelines aim to shift clinicians away from use of acid suppression toward empirical 2-week trials of hypoallergenic formula in many cases.³

We agree with Mitre et al¹ that acid-suppressive medications are frequently prescribed early in infancy despite little evidence supporting their use, and that there is growing evidence that effects of acid-suppression mediated by the microbiome may have lasting effects. We also strongly agree with the need for carefully controlled prospective studies to directly assess the potential effects of acid suppression on the developing microbiome and pediatric health. However, until those prospective studies are done, we suspect it will be impossible to tease out the true association.

Victoria Martin, MD

Corinne Keet, MD, MS, PhD

Qian Yuan, MD, PhD

Author Affiliations: Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Massachusetts General Hospital, Boston (Martin, Yuan); Division of Pediatric Allergy and Immunology, Johns Hopkins Hospital, Baltimore, Maryland (Keet).

Corresponding Author: Qian Yuan, MD, PhD, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114 (qyuan@mgh.harvard.edu).

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1. Mitre E, Susi A, Kropp LE, Schwartz DJ, Gorman GH, Nylund CM. Association between use of acid-suppressive medications and antibiotics during infancy and allergic diseases in early childhood. *JAMA Pediatr*. 2018;172(6):e180315-e180318. doi:10.1001/jamapediatrics.2018.0315

2. Martin VJ, Seay HL, Virkud Y, Keet C, Shreffler WG, Yuan Q. Prospective incidences and the relationship between allergic proctocolitis and IgE-mediated food allergies in early childhood. *J Allergy Clin Immunol*. 2017;139(2):AB274. doi:10.1016/j.jaci.2016.12.883

3. Koletzko S, Niggemann B, Arato A, et al; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Diagnostic approach and management of cow’s-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr*. 2012;55(2):221-229. doi:10.1097/MPG.0b013e31825c9482

Letters

COMMENT & RESPONSE

Antibiotics and Acid-Suppressing Medications in Early Life and Allergic Disorders

To the Editor The study by Mitre et al¹ is concerning given incomplete acknowledgment of limitations and questionable accuracy of associations between antireflux and antibiotic use independently increasing the risk of developing allergic diseases.¹ Using *International Classification of Diseases, Ninth Revision* codes to indicate a diagnosis of allergic conditions is often inaccurate without additional encounter-level details verifying a history consistent with the condition and confirmatory testing. These diagnoses were not linked to allergist referral and confirmatory coding, evidence of allergen sensitization, abnormal pulmonary function testing, or treatment of the diagnosis.² This raises concerns of misspecified associations with risk.

The theory that antireflux or antimicrobial treatment may adulterate the microbiome, predisposing development of an allergic milieu, is hypothetical, lacking human evidence of causality, but is of interest in food allergy.² However, Mitre et al¹ do not show universally elevated risk for all food allergies, just some. This makes little sense and lacks biologic plausibility for how microbiome alterations would selectively predispose to only certain food allergies. It is unclear whether these food allergy associations were controlled for other potentially relevant risks, such as family history, prenatal exposures, breastfeeding, vitamin D levels, and timing of introduction of solid foods, or worse, influenced by reverse causality from misdiagnosis.²

Beyond food allergy, the median ages of diagnosis for most of the conditions are suspiciously low, indicative of misdiagnosis. Antibiotic allergy is notoriously overdiagnosed in young children, whereas nonallergic rashes are often misclassified as allergies. Before age 5 years, transient viral-induced wheezing is difficult to distinguish from asthma, and allergic rhinitis with documentable sensitization is uncommon. Chronic urticaria has strict criteria and is very uncommon in children.³

While the authors admit some limitations of their retrospective study design, we feel many more could have been emphasized. Most importantly, this study design cannot prove the infants actually ingested these medications and for how long. This is not unimportant and may completely confound their conclusions.

There is danger in taking these associations too literally, given potentially inaccurate diagnosis and unknown exposure history. While we agree that reflux in infants is over-treated and antibiotics overprescribed (among other conditions that may also be overdiagnosed in children),^{4,5} there is potential for harm if parents refuse these treatments when truly indicated, and a more fruitful approach is for prescribers to at least agree on what “situations of clear clinical benefit”¹ actually means. The potential for spawning irre-

versible public opinion regarding unsubstantiated causes of allergic diseases cannot be underestimated.

Matthew Greenhawt, MD, MBA, MSc
David Stukus, MD
Edmond S. Chan, MD

Author Affiliations: Section of Allergy and Immunology, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora (Greenhawt); Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus (Stukus); BC Children's Hospital, Division of Allergy and Immunology, Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada (Chan).

Corresponding Author: Matthew Greenhawt, MD, MBA, MSc, Section of Allergy and Clinical Immunology, Children's Hospital Colorado, University of Colorado School of Medicine, 13123 E 16th Ave, PO Box 518, Anschutz Medical Campus, Aurora, CO 80045 (matthew.greenhawt@childrenscolorado.org).

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Letters

COMMENT & RESPONSE

Antibiotics and Acid-Suppressing Medications in Early Life and Allergic Disorders

To the Editor We read with interest the Mitre et al article¹ describing associations between acid-suppressive medications, antibiotics, and subsequent pediatric allergic disease.¹ Because histamine-2-receptor antagonists (H2RAs) are commonly prescribed for children with gastroesophageal reflux disease (GERD), the authors presented analyses of associations between H2RAs and allergic diseases, including food allergy, for all children, and only those who received a diagnosis of GERD. However, compared with any food allergy or individual foods among children given H2RAs, milk allergy has both a higher incidence and higher hazards ratios, which may partially drive the strong association between H2RAs and “any food allergy.” Infants with milk allergy often tolerate milk by early childhood, an observation that the authors did not consider herein. Because the ability to consider tolerance may not have been possible in a health care database study, an analysis excluding children with only milk allergy would have been interesting. Similarly, we would have liked to have seen results for individual food allergies among the children with GERD.

The authors report a slight but significant association between H2RA and “any nonfood allergy”¹ among the GERD group, an outcome not considered for all children receiving H2RAs. However, we would have also appreciated results of associations between H2RAs and allergic disease outcomes among children who did not receive a diagnosis of GERD.

Premature and cesarian section births are on the causal pathway that predisposes infants to subsequent allergic diseases.² Mitre et al¹ report that children born prematurely or via cesarean delivery were associated with a significantly increased risk for allergic disease vs those born without these conditions. The authors adjusted for these and other confounders in the final model. However, analyses adjusted solely for cesarean delivery and prematurity, or a sensitivity analy-

sis of children born with these conditions, would have been informative, given the predominance of these conditions in the H2RA group.

Although the authors conclude that antibiotics and acid-suppressive medications increase the risk of allergic conditions in childhood, the allergic diagnoses included in this retrospective cohort include conditions with differing pathophysiologic mechanisms, such as immunoglobulin E (IgE)-mediated conditions (food allergy) and T-cell-mediated conditions (contact dermatitis).³ As a result, this study suggests a similar predisposing mechanism for several conditions that are pathophysiologically distinct. We appreciate the authors' conclusion that acid-suppressive and antibiotic medications should be used judiciously in infancy and would look forward to any additional comments the authors could provide about the issues discussed here.

Jennifer L. P. Protudjer, PhD
Elissa M. Abrams, MD, FRCPC

Author Affiliations: Karolinska Institutet, Stockholm, Sweden (Protudjer); University of Manitoba, Winnipeg, Manitoba, Canada (Abrams).

Corresponding Author Elissa M. Abrams, MD, FRCPC, Section of Allergy and Clinical Immunology, Department of Pediatrics, University of Manitoba, FE125-685 William Ave, Winnipeg, MB R3E 0Z2, Canada (elissa.abrams@gmail.com).

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Letters

COMMENT & RESPONSE

Antibiotics and Acid-Suppressing Medications in Early Life and Allergic Disorders

To the Editor With great interest we read the article by Mitre et al.¹ This study is, to our knowledge, the largest cohort in which the association between antibiotic treatment in early life and later allergic disorders is investigated, and we congratulate the authors for the extensive analyses of this cohort. For the cohort of Mitre et al,¹ 2 specific exclusion criteria drew our attention: the exclusion of children with allergic conditions in the first 6 months, as well as initial birth stay greater than 7 days. The first exclusion criterion may lead to the underestimated prevalence of allergic conditions, especially atopic dermatitis, which often occurs before age 6 months.² Although we do understand that allergic conditions occurring before 6 months may obscure the effect of medication given after 6 months of age, we would like to know whether the authors can indicate how this may have changed the outcome of their study. For the second exclusion criterion, we would like to know whether this means that all infants who received antibiotics at birth for suspected neonatal infection were excluded. In 2018, we published the outcome of the Intestinal Microbiota Composition After Antibiotic treatment in Early Life study in which children who received antibiotics at birth were compared with children who did not.³ We found that antibiotics given in the first week of life significantly influence the outcome of wheezing in the first year of life. Moreover, we found a trend toward a higher incidence of allergic sensitization at age 1 year. Therefore, Mitre et al¹ may have underestimated

the risk for allergic disorders by excluding neonates with an initial birth stay greater than 7 days.

This study by Mitre et al¹ contributes to the mounting evidence that early life is a critical period in which gut microbiome disturbances by medications, such as antibiotics and acid suppressants, can have a profound association with the development of immune-related disorders. It will be very interesting in the near future to investigate more in depth the role of type, timing, and route of administration of antibiotic treatment or other medications known to alter the gut microbiome on the prevalence of allergic disorders.

Berthe C. Oosterloo, MD

Arine M. Vlieger, MD, PhD

Ruurd M. van Elburg, MD, PhD

Author Affiliations: Emma Children's Hospital, AMC, Amsterdam, the Netherlands (Oosterloo, van Elburg); St Antonius Hospital, Nieuwegein, the Netherlands (Vlieger); Nutricia Research, Utrecht, the Netherlands (van Elburg).

Corresponding Author: Ruurd M. van Elburg, MD, PhD, Department of Early Life Nutrition, Emma Children's Hospital, AMC, Meibergdreef 9, Room H7-252, Amsterdam 1105 AZ, the Netherlands (r.m.vanelburg@amc.uva.nl).

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Letters

COMMENT & RESPONSE

In Reply We thank the respondents to our article¹ for their insights. Greenhawt et al refer to our use of *International Classification of Diseases, Ninth Revision (ICD-9)* codes as the sole means of diagnosing allergy and a lack of adjustment for a number of risk factors for allergy, including family history, prenatal exposures, breastfeeding, vitamin D levels, and timing of solid food introduction. We agree that these are important limitations. Greenhawt et al propose that our study makes little sense biologically because it does not show elevated risk for all food allergies. Our study actually observed an increased risk (adjusted hazard ratios >1) for all subsets of food allergy. These risks were statistically significant for all subsets other than seafood in children who had received antacid therapies and seafood and peanuts in children who had received antibiotics as infants. Seafood allergy was the least commonly diagnosed food allergy in our study cohort. We disagree with Greenhawt et al that there is little human evidence that alterations in the microbiome may predispose to allergy because several studies have shown this association in humans.^{2,3}

Greenhawt et al state that the median ages of diagnosis for most of the conditions are “suspiciously low.” The median ages of diagnosis were low because the cohort was young (median follow-up of 4.6 years from birth [IQR, 2.5-7.9 months]). Greenhawt et al state that there is potential harm if parents refuse treatments, such as antibiotics or antacid medications. We agree. However, our study found that more than 8% of all infants were prescribed an antacid medication in the first 6 months of life. This certainly represents preventable physician-directed antacid overuse owing to overmedicalization of physiologic infant reflux. Expert opinion and new guidelines provide indications for use of antacid medications and advise the use of nonpharmacologic measures as initial therapy for most infants with regurgitation.^{4,5}

We agree with Oosterloo et al that some of our exclusion criteria may have resulted in underestimation of allergy risk. We also agree with Martin et al that reverse causality may have played a role for some allergic diagnoses, especially food allergy, and agree that this limitation is not completely overcome by our subgroup analysis of infants with gastroesophageal reflux disease (GERD). That stated, we did exclude children who received a diagnosis of either allergy to milk products or allergic gastroenteritis and colitis.

We performed additional analyses of the data as requested by Protudjer and Abrams. Risks for allergy after exclusion of children with only milk allergy were very similar to those of the full cohort. Among children who did not receive a diagnosis of GERD, adjusted hazard ratios for histamine-2-receptor antagonists were 1.52 (95% CI, 1.37-1.68) for any food allergy and 1.12 (95% CI, 1.09-1.16) for any nonfood allergy. Ad-

Table. aHRs for Specific Food Allergies in Children Who Received a Diagnosis of Gastroesophageal Reflux Disease^a

Food Allergy Type	aHR (95% CI)		
	Antibiotics	H2RAs	PPIs
Cow's milk (n = 1176)	1.16 (1.02-1.32)	1.38 (1.23-1.56)	2.01 (1.76-2.31)
Peanut (n = 798)	0.94 (0.80-1.11)	1.39 (1.11-1.75)	1.18 (0.96-1.45)
Egg (n = 502)	0.98 (0.80-1.20)	1.34 (1.12-1.60)	1.34 (1.06-1.70)
Seafood (n = 167)	0.83 (0.57-1.20)	0.85 (0.62-1.16)	1.11 (0.69-1.78)
Other food (n = 3137)	1.01 (0.93-1.10)	1.55 (1.39-1.73)	1.83 (1.57-2.13)

Abbreviations: aHR, adjusted hazard ratio; H2RA, histamine-2-receptor antagonists; PPI, proton pump inhibitor.

^a Adjusted hazard ratios for specific food allergies in children who received a diagnosis of gastroesophageal reflux disease during infancy (n=96 684) and given antibiotics, H2RAs, or PPIs prior to 6 months of age (antibiotics n=22 626, H2RAs n=49 681, PPIs n=12 128, and no drug exposure n=33 634).

justed hazard ratios for individual food allergies in the subset of children with GERD diagnosed before 6 months of age are presented in the **Table** below. The fact that the allergic disease outcomes we evaluated develop by different immunological mechanisms does not render the conclusions of the study invalid because, to some extent, all of these allergy effector pathways can be controlled by immunoregulatory pathways. There is mounting evidence that the microbiome plays a major role in establishment of immunoregulatory networks during infancy.⁶

Edward Mitre, MD
Apryl Susi, MS
Cade M. Nylund, MD

Author Affiliations: Department of Microbiology and Immunology, F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland (Mitre); Department of Pediatrics, F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland (Susi, Nylund).

Corresponding Author: Edward Mitre, MD, Department of Microbiology and Immunology, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd, Bethesda, MD 20814 (edward.mitre@usuhs.edu).

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