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Early-life antibiotic exposure and childhood food allergy: A systematic review



To the Editor:

Use of antibiotics in children has increased over the last few decades. Concurrent with this, there has also been a dramatic increase in the prevalence of allergic diseases, including food allergy. A large study in Australia reported that nearly one in five 12-month-old infants is sensitized to at least 1 food, and more than 10% have challenge-proved food allergy.¹ Several studies suggest a relationship between antibiotic exposure and allergic disease, particularly asthma and eczema.² Antibiotics might promote the development of allergy by interfering with the microbiome-dependent normal maturation of the immune system through an imbalance in T-cell maturation favoring a T_H2 cell response.

In this systematic review we aimed to identify studies investigating the association between antibiotic exposure and food allergy and the factors affecting this relationship.

A systematic search of Medline, Embase, and PubMed was done in February 2019 to identify studies that investigated the association between early-life antibiotic exposure and childhood food allergy (Fig 1). Articles were included if they evaluated an association between antibiotics and food allergy in children (0-18 years of age). Food allergy was defined as either (1) reported symptoms directly related to food or drink intake together with a positive IgE blood test or skin prick test result and/or positive oral food challenge result or (2) diagnosis of food allergy by a physician. Articles were excluded if they used alternative definitions for food allergy (eg, skin prick test results only or outcome based on parental questionnaire only; Fig 1).

Of 1058 unique articles identified in the original systematic search (February 2019), 6 relevant articles met the inclusion criteria (2 prospective^{3,4} and 4 retrospective⁵⁻⁸). Of these, 4 articles (1 prospective⁴ and 3 retrospective⁶⁻⁸) found a significant association between early-life antibiotic exposure and food allergy in childhood. All 4 attempted to adjust for protopathic bias but did not correct for all potential factors. Two of the 4 studies found the association correlated with antibiotic exposure (number of courses). Two studies did not find an association between antibiotic exposure and food allergy. The results are outlined in Table 1.³⁻⁸

Overall, our systematic review found evidence to suggest an association between early-life antibiotic exposure and childhood food allergy. However, this association was found in only 4 of 6 studies. There are several potential explanations for the discrepancies in the results of the 6 studies.

First, study design and methods differed between the studies. In particular, the number of participants varied, and one study (with only 291 participants) that did not find a significant association between antibiotic exposure and allergy might have been insufficiently powered to find a difference.⁵

Second, the definition of food allergy outcomes differed between studies. Of the 4 studies that found a significant association, in 3 studies food allergy was defined by using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, which do not distinguish between food intolerance and food allergy.⁶⁻⁸ The fourth study that found a significant association defined food allergy by using

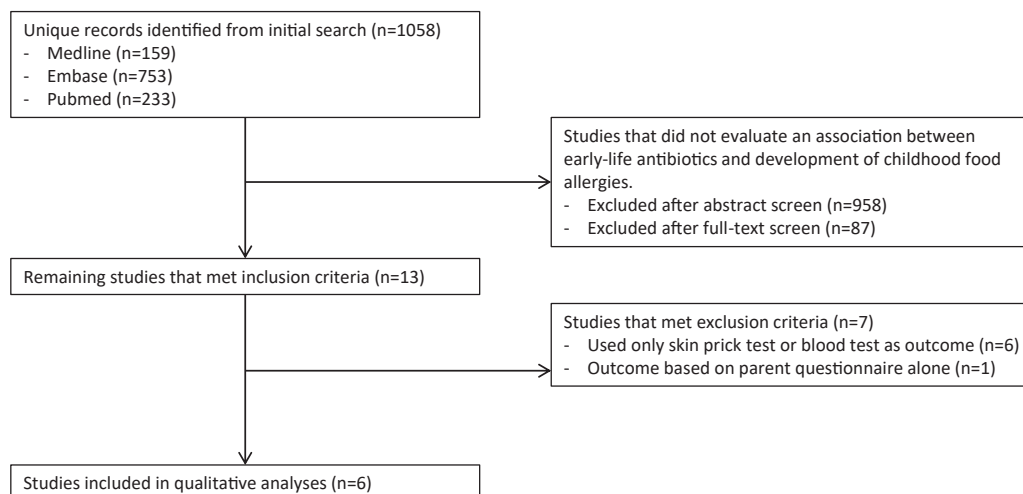


FIG 1. Details of systematic literature search. Search terms were as follows: (asthma* or "food allergy" or "food hypersensitivity*" or "atopic dermatitis" or "hay fever" or "allergic rhinitis" or hayfever) and (antibiotic* or antimicrobial or antimicrobial or antibacterial or anti-bacterial) and (exposure or prescription* or dose-response or "dose response" or riskfactor* or "risk factor" or "risk factors" or prevalence or peri-natal or perinatal or post-natal or postnatal or "disease association") and (child or children or childhood or pediatric* or paediatric* or infant* or newborn* or neonat* or toddler* or girl or girls or boy or boys or preschooler* or preschooler* or adolescent* or youth* or teen or teens or teenage*).

a more robust definition, namely self-reported allergic reaction (using a standardized interview) plus a positive IgE test or skin prick test result.⁴ One of the 2 studies that did not find a significant association also used ICD-9-CM codes but included the results of IgE or skin prick tests to define food allergy.⁵ The other study that did not find an association used parent-reported allergic reaction (interview) plus a report of a positive blood IgE test or positive skin prick test result.³

Among the 4 studies that found an association, the extent to which protopathic bias was considered, and the adjustment models used differed, which affects the interpretation of their results. Because IgE-mediated food allergies have been associated with concomitant IgE-mediated allergic diseases,⁹ 3 studies⁶⁻⁸ adjusted for other allergic diseases. In 2 studies the association between antibiotic exposure and food allergy remained unchanged,^{6,8} whereas in the other study the association between antibiotic exposure and nonmilk food allergy was no longer significant.⁷ This suggests that the other allergy diagnoses accounted for the observed association between antibiotics and food allergy in one of the studies. However, exclusion of cases that have other allergic diseases could also lead to an underestimation of a clinically relevant effect of antibiotic exposure on IgE-mediated food allergy, even if the latter is a secondary or concomitant effect of another IgE-mediated allergic disease.

One of the studies accounted for the age of antibiotic exposure and found the association to be similar across different age groups.⁷ However, although remaining statistically significant, the association between antibiotic use and food allergy weakened as the time between antibiotic exposure and diagnosis increased.

The association between antibiotics and food allergies is likely to be multifactorial. Because the microbiome plays a critical role in development of the immune system, antibiotic-induced changes in the microbiome are likely to be the predominant

mechanism by which antibiotic exposure influences the risk of food allergy.¹ As a result of their stronger influence on the microbiome, broad-spectrum (in contrast to narrow-spectrum) antibiotics are likely to have a greater influence on the development of the immune system and allergic disease. In support of this, the 2 studies that differentiated between the effect of antibiotic type both found the strongest association with broad-spectrum antibiotics.^{6,7}

In conclusion, there is some evidence to support the hypothesis that early-life antibiotic exposure is associated with the development of childhood food allergy. However, an association was not consistently found in all studies. Whether this association is causal or correlational remains uncertain because of inconsistencies between studies in design and the inability to completely exclude protopathic bias. It also remains uncertain whether any association is only applicable in certain children or is dependent on antibiotic exposure (number of courses, dose, duration, and type), age of antibiotic exposure, or spectrum of antibiotic activity. Future prospective studies should minimize protopathic bias (by excluding antibiotic exposure close to the time of allergy diagnosis and accurately recording the indication for antibiotic use), which is correct for other allergic diseases and assess the role of number of courses, dose, duration, and type (narrow vs broad spectrum) of antibiotic exposure.

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TABLE I. Summary of studies that have investigated the association between early-life exposure to antibiotics and childhood food allergy

First author, year of publication	Study design/ country	No. of participants/ age group	Antibiotic exposure	Outcome definition	Results	Relevant allergic factors included in adjusted results	Linear association observed	Antibiotic class specified
Eggesbo et al, ³ 2003	Prospective cohort/ Norway	2803/ 0-2.5 y	First 6 mo of life	Parent-reported immediate reaction to egg plus positive IgE test result or positive OFC result*	OR, 1.4 (95% CI, 0.6-3.3); aOR, 1.5 (95% CI, 0.6-3.7)	None	No	No
Risnes et al, ⁴ 2011	Prospective cohort/ United States	1401/ 0-6 y	First 6 mo of life	Parent-reported allergic reaction (interview) plus report of a positive blood IgE test or positive SPT result	OR, 1.93 (95% CI, 1.38-2.71); aOR, 1.59 (95% CI, 1.10-2.28)	LRI, parental asthma	No	No
Dowhower Karpas et al, ⁵ 2012	Retrospective case-control/ United States	99 cases and 192 control subjects/ 0-18 y	First 18 y of age	ICD-9-CM codes plus positive IgE test or positive SPT result or pediatrician-diagnosed food allergy	OR, 1.35 (95% CI, 0.680-2.68)	None	No	No
Love et al, ⁶ 2016	Retrospective case-control/ United States	1504 cases and 5995 control subjects/ 0-3 y	First year of life	Physician's diagnosis with matching ICD-9-CM code	≥1 AB course vs none: OR, 1.22 (95% CI, 1.08-1.37); ≥1 AB course vs none: aOR, 1.21 (95% CI, 1.06-1.39); >5 AB courses vs none: aOR, 1.64 (95% CI, 1.31-2.05)	Asthma, eczema, wheeze	Yes; increase in aOR	Yes
Hirsch et al, ⁷ 2017	Retrospective case-control/ United States	484 cases and 598 control subjects/ 2 mo-7 y	Milk allergy: up to 30 d before diagnosis† Non-milk food allergy: 0-12 mo†	Outpatient, inpatient, or emergency department encounter or medication order plus ICD-9-CM codes	Milk allergy diagnosed up to 300 d† 1-2 AB courses vs none: OR, 1.43 (95% CI, 0.97-2.09); ≥3 AB courses vs none: OR, 2.39 (95% CI, 1.25-4.59); 1-2 AB courses vs none: aOR, 1.35 (95% CI, 0.84-2.17); ≥3 AB courses vs none: aOR, 3.65 (95% CI, 1.75-7.60) Non-milk food allergy diagnosed up to 700 d† 1-2 AB courses vs none: OR, 1.27 (95% CI, 0.96-1.69); ≥3 AB courses vs none: OR, 1.95 (95% CI, 1.38-2.75); 1-2 AB courses vs none: aOR, 1.01 (95% CI, 0.66-1.55); ≥3 AB courses vs none: aOR, 1.40 (95% CI, 0.85-2.33)	Infants with other allergic diseases	Yes; increase in OR	Yes
Li et al, ⁸ 2019	Retrospective case-control/ United States	500,647 antibiotic users and 500,647 antibiotic non-users/ 0-4 y	First year of life	ICD-9-CM code	≥1 vs none: HR, 1.40 (95% CI, 1.34-1.45) 1 vs none: HR, 1.49 (95% CI, 1.41-1.58); ≥2 vs none: HR, 1.31 (95% CI, 1.24-1.39) ≥1 vs none: aHR, 1.46 (95% CI, 1.38-1.55)	Rhinitis, dermatitis, toxic effect, and other adverse food reactions	Yes; no increase in HR	No

AB, Antibiotic; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; HR, hazard ratio; LRI, lower respiratory tract infection; OFC, oral food challenge; OR, odds ratio; SPT, skin prick test.

*Second outcome measure (questionnaire-based symptoms) did not fit the inclusion criteria.

†Multiple other results were presented in the original article.

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Detection of KIT D816V mutation in patients with severe anaphylaxis and normal basal tryptase—first data from the Anaphylaxis Registry (NORA)



To the Editor:

Anaphylaxis is the most severe and potentially life-threatening systemic allergic condition. Insect venom, food, and drugs are the main elicitors.

The diagnosis of anaphylaxis is clinically based on symptoms on exposure to a potential elicitor. Despite improved diagnostic measures including the use of recombinant allergens for IgE diagnostics, reliable biomarkers for the diagnosis, prediction, and risk stratification of anaphylaxis are lacking.¹ The only marker routinely available is total serum tryptase level, which rapidly increases during the acute phase of an anaphylactic reaction. However, total serum tryptase level should be assessed outside the anaphylactic episodes in all patients with a previous moderate to severe allergic reaction. It can serve as a risk indicator for consecutive severe anaphylactic reactions, in particular in patients with insect venom allergy.²

Patients with an increased baseline serum tryptase level may also suffer from an underlying mastocytosis or mast cell activation syndrome.³ Mastocytosis is characterized by an accumulation of mast cells in various tissues. Adult patients mostly suffer from an indolent systemic mastocytosis, in which the skin, the gastrointestinal tract, and the bone marrow are most prominently affected. In more than 95% of patients, the activating KIT mutation D816V is identified as an underlying cause of mastocytosis. Because of the clonal expansion of mast cells, mastocytosis can promote the onset and severity of allergic reactions. Thus, mastocytosis is one of the most important risk factors for severe anaphylaxis, which has recently been confirmed by data

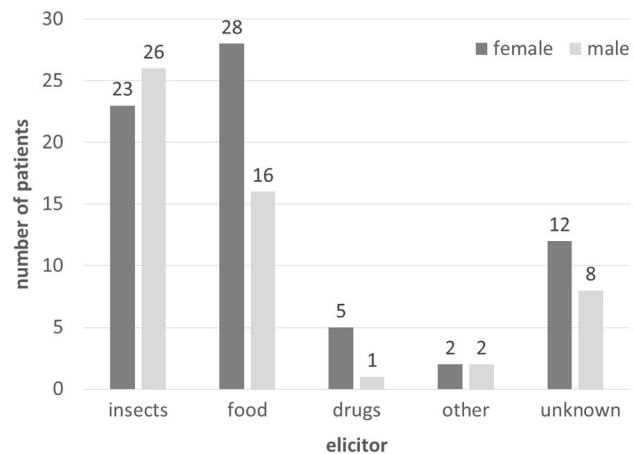


FIG 1. Elicitors and sex distribution within the study cohort (n = 123).

from the European Anaphylaxis Registry.⁴ Despite this striking evidence, mastocytosis is often underdiagnosed in patients with anaphylaxis. One reason for this is that the phenotype of mastocytosis in patients with anaphylaxis is often clinically inapparent because patients may have no or very discrete skin lesions and/or nonelevated basal serum tryptase levels. In particular, when baseline tryptase level is normal, which applies to a subgroup of patients with mastocytosis,⁵ a bone marrow biopsy is routinely not performed to rule out mastocytosis. Thus, patients with severe anaphylaxis may not be diagnosed regarding an underlying mastocytosis because of the absence of clinical signs and the lack of elevated baseline tryptase levels. Today, the KIT D816V mutation can be detected in the peripheral blood with high sensitivity by a PCR-based assay.⁶ In this study, we aimed to determine the frequency of the KIT D816V mutation in a large cohort of patients with severe anaphylaxis, but normal baseline tryptase levels.

A total of 123 patients from the Anaphylaxis Registry were identified (Fig 1) and blood samples were screened for KIT D816V mutation according to the method described elsewhere.⁶ The Ethics Committee at Charité - Universitätsmedizin Berlin (EA01/079/06) approved the study and all patients gave their written informed consent.

The KIT D816V mutation was detected in 6 of the 123 patients (5%) (Table I). For patients 1, 4, 5, and 6, the elicitor yellow jacket was confirmed by history, skin prick test, and specific IgE and venom immunotherapy (VIT) was initiated. Patients 2 and 3 had most likely food-induced anaphylaxis because shrimp and soy/celery were suspected. The workup including oral food challenges was offered to both patients, but they refused. Skin prick test results were positive (shrimp 4 mm, soy 4 mm/celery 5 mm), but specific IgE was negative (Table I). Both patients had low to normal total IgE levels. Low total IgE level is a known phenomenon in patients with mastocytosis.⁷

The patients with a positive screening result for KIT D816V mutation were reevaluated regarding an underlying mastocytosis or mast cell activation syndrome.³ A bone marrow assessment was offered to the patients, but it was initially rejected by all patients. Moreover, an annual monitoring of complete blood count, serum tryptase level, and a bone scan every 2 years were recommended. A lifelong VIT was recommended to the patients with venom allergy.

Five of the 6 patients with positive KIT D816V mutation had no skin lesions of mastocytosis. Our preliminary data support