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Lack of Clinical Hypersensitivity to Penicillin Antibiotics in Common Variable Immunodeficiency

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To the Editor

Common variable immunodeficiency (CVID) is a heterogeneous primary immunodeficiency defined by low serum immunoglobulins (low IgG and low IgA and/or IgM) and poor specific antibody response to vaccines [1]. Although prevalence of IgE-mediated allergic disease in CVID appears to be uncommon, there has been no prior report on the presence or rate of IgE-mediated drug allergy in the CVID population. More specifically, no study has been conducted in CVID to evaluate beta-lactam hypersensitivity.

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Although it is not part of current diagnostic criteria for CVID [1], many patients with CVID have low or undetectable levels of IgE [2]. Rates of specific IgE (serum and/or skin testing) measurement vary from 3 to 16% [2, 3] while as many as 82% of patients with CVID report symptoms consistent with allergies [2]. Because patients with CVID have low levels of total and antigen-specific IgE, the presence of allergic diseases should theoretically be rare or non-existent. Based on these prior observations, we hypothesized that patients with CVID would not have IgE-mediated hypersensitivity reactions to beta-lactam medication.

We set out to determine the rates of self-reported beta-lactam allergy in the CVID population and test for clinical hypersensitivity with skin testing and in-office dose challenge. The study was approved by the Children's Hospital of Wisconsin Institutional Review Board. Funding was provided by the Division of Allergy and Clinical Immunology. All patients were recruited from July 2015 to June 2016. Informed consent was obtained from all individual participants included in the study.

Patients were selected based on diagnosis of CVID by internationally agreed upon diagnostic criteria [1]. Patients were then screened for self-reported beta-lactam (ex: penicillin, amoxicillin, ampicillin) allergy in the hospital electronic medical record. Patients were excluded from the study if they had chronic severe respiratory compromise (supplemental oxygen requirement or dependence on positive pressure ventilation), beta-blocker use, pregnancy, history of non-IgE-mediated beta-lactam reactions, or prior exclusion of beta-lactam hypersensitivity.

Eligible patients underwent a two-step skin testing procedure with PRE-PEN® (AllerQuest LLC, Plainville, CT) and penicillin G per the American Academy of Allergy, Asthma and Immunology (AAAAI) drug allergy practice parameters [4]. If intradermal testing was negative, a single dose challenge of 500 mg amoxicillin was administered with a 30-min observation period. If intradermal testing was positive, as defined as wheal formation of >3 mm larger than the saline control, a two-dose oral challenge was performed excluding patients with a history of life-threatening reactions. The two-dose challenge (10%/90%) was performed with 50 mg amoxicillin, 30 min observation followed by 450 mg and additional observation.

The medical records of 100 patients with CVID were reviewed, 33 (33%) self-reported beta-lactam allergy. Four of the 33 patients reported non-IgE-mediated symptoms (nausea/vomiting without other systemic symptoms or local irritation with IV form), and two patients were skin-tested and/or drug challenged showing no evidence of beta-lactam hypersensitivity. Excluding these 6 patients, 27 patients had possible beta-lactam hypersensitivity. Five patients were excluded based on standard skin testing precautions (respiratory compromise ($n = 3$), beta-blocker use ($n = 2$)), and seven patients were unavailable for testing due to geographic limitations.

Fifteen patients (age range 17–74 years) underwent a combination of skin testing and penicillin drug challenge (Table 1). All patients with available data in the medical record (12/15) had an undetectable (<2 mg/dL) serum IgE level. Initial self-reported reactions to beta-lactam antibiotics occurred from infancy to the age of 71. Clinical manifestations

reported were rash (47%), hives (33%), swelling (7%), or unknown (20%). Twelve patients (n = 12, 80%) self-report that their beta-lactam reaction occurred prior to the diagnosis of CVID. Two patients (patients 5 and 6) reported their reaction following the diagnosis of CVID. Thirteen patients tested negative with skin testing and passed in-office oral challenge with no adverse events. One patient reported nausea and vomiting hours after administration with no other event. Two patients (patients 2 and 6) had positive intradermal testing to PRE-PEN®, both tolerated graded challenge with no adverse events.

To further evaluate the prevalence of reported beta-lactam allergy in a broader population of patients with CVID, we queried the United States Immunodeficiency Network (USIDNET) patient registry dataset in March 2016. The USIDNET registry includes 950 patients with CVID. Drug allergy was reported in 35%(n = 329) and beta-lactamallergy in 7% (n = 67). The most common beta-lactam reported is penicillin (73%) followed by amoxicillin (18%), amoxicillin-clavulanic acid (12%), ampicillin (1%), and piperacillin (1%). Of those with reported symptoms, rash/dermatitis is the most commonly reported reaction (19%), followed by hives, nausea/vomiting, angiedema/swelling, asthma, with few patients (3%) reporting anaphylaxis. The self-reported prevalence of beta-lactam allergy in the USIDNET cohort is similar to that reported in the general population (10%) [4] but less than in our cohort of patients. The reasons for this discrepancy are unknown.

This is the first report of the evaluation of beta-lactam drug allergy in patients with CVID. We found that although self-reported allergy to beta-lactam antibiotics was high in our cohort of patients, no patient demonstrated true clinical hypersensitivity to beta-lactams by objective testing. These findings are consistent with the absence of IgE in all patients in which serum IgE was measured and with prior reports in CVID demonstrating low serum total and specific IgE as well as low skin prick test reactivity [2, 3].

We believe potential implications of these findings are important from a patient management perspective and in terms of financial costs to the health care system. Patients with CVID suffer from recurrent sinopulmonary infections. The exclusion of beta-lactams may lead to the use of less-efficacious antibiotics often with increased cost and side effects as well as increased selection for drug-resistant organisms. The financial burden due to altered care to inpatients with self-reported beta-lactam allergy within Kaiser Permanente in southern California alone from 2010 to 2012 was nearly $65,000,000, which could be substantially mitigated by the use of skin testing at a cost of approximately $3000 [5].

The major limitation of this study is the small sample size. Although we manage a relatively large cohort of CVID patients (n = 100), the number of patients with possible penicillin allergy that were available for testing was relatively small (n = 15). This is a more general problem in the evaluation of patients with orphan diseases such as CVID, which has a prevalence estimated at 1:10,000 to 1:100,000 [1]. Ninety-percent of patients in the general population who report a penicillin (PCN) allergy are able to tolerate PCN. Thus, this study is underpowered to determine if true penicillin allergy in CVID is less than found in the general population. However, we hypothesize true penicillin allergy will be extraordinarily low in patients with CVID given the low serum IgE and lack of antigen-specific IgE in patients with CVID.

In summary, IgE-mediated hypersensitivity to beta-lactam antibiotics appears to be rare when objective testing is performed. Based on these results, we believe that patients with CVID and a history of beta-lactam hypersensitivity should be evaluated by skin testing and in-office oral challenge. Institution of this objective testing could improve the management of infections and decrease the economic costs associated with antibiotic usage in patients with CVID.

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References

1. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International consensus document (ICON): common variable immunodeficiency disorders. J Allergy Clin Immunol Pract. 2016; 4(1):38–59. [PubMed: 26563668]
2. Agondi RC, Barros MT, Kokron CM, Cohon A, Oliveira AK, Kalil J, et al. Can patients with common variable immunodeficiency have allergic rhinitis? Am J Rhinol Allergy. 2013; 27(2):79–83. [PubMed: 23562193]
3. Agondi RC, Barros MT, Rizzo LV, Kalil J, Giavina-Bianchi P. Allergic asthma in patients with common variable immunodeficiency. Allergy. 2010; 65(4):510–515. [PubMed: 19839975]
4. Joint Task Force on Practice P, American Academy of Allergy A, Immunology, American College of Allergy A, Immunology, Joint Council of Allergy A. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010; 105(4):259–273. [PubMed: 20934625]
5. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: a cohort study. J Allergy Clin Immunol. 2014; 133(3):790–796. [PubMed: 24188976]

Table 1

Patient data and testing results

Patient ID	Age	Gender	Age CVID diagnosis	Age allergy reported	Antibiotic given	Reaction	IgE (kU/L)	Skin testing	Dose challenge
1	17	F	8	2	Beta-lactam	Hives, swelling	<2	Negative	Negative
2	19	F	2	3	Augmentin	Rash	<2	Positive	Negative
3	50	M	42	30	Beta-lactam	Rash	<2	Negative	Negative
4	49	M	38	16	Penicillin	Hives	<2	Negative	Negative
5	74	M	71	72	Amoxicillin	Unspecified	<2	Negative	Negative
6	47	M	42	44	Amoxicillin	Hives	<2	Positive	Negative
7	51	F	45	41	Amoxicillin	Hives	<2	Negative	Negative
8	17	F	11	3	Augmentin	Rash	<2	Negative	Negative
9	52	F	28	Infant	Penicillin	Rash	<2	Negative	Negative
10	35	M	22	Infant	Penicillin	Unspecified	n/a	Negative	Negative
11	42	F	35	27	Amoxicillin	Skin redness	n/a	Negative	Negative
12	45	F	38	20	Amoxicillin	Rash	n/a	Negative	Negative
13	39	F	38	20	Amoxicillin	Rash	<2	Negative	Negative
14	52	F	35	32	Amoxicillin	Rash	<2	Negative	Negative
15	50	F	25	20	Amoxicillin	Hives	<2	Negative	Negative

Patients are identified by their ID assigned in chronological order of testing. Their current age, age at the time of CVID diagnosis, and age at the time of beta-lactam allergic reaction are reported in years unless specified otherwise. The antibiotic that elucidated the given reaction is reported as the patients recalled. If they were unsure of their age, the antibiotic, or the reaction, it is listed as such. Antibiotics are reported as “Beta-lactam” if the specific medication was not recalled, reactions as “Unspecified.” The most recent serum IgE is reported if it is known

Abbreviations: n/a – not available