

RESEARCH LETTER

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Specific IgE to penicillin minor determinants in patients with suspected penicillin allergy

To the Editor,

Risk stratification of patients with suspected penicillin allergy is an important tool in identifying patients with immediate type reactions, who may carry a high risk of a reaction during allergy investigations with skin testing and/or drug provocation testing. In this patient category in-vitro tests such as measurement of specific IgE to penicillins may be a safer first step investigation and this has been recommended in recent European Guidelines.¹ A recent meta-analysis on the accuracy of specific IgE as a diagnostic test in penicillin allergy, including studies of both immediate and non-immediate reactions, reported a high specificity (97.4%) but low sensitivity (19.3%).² Due to the reported low sensitivity, specific IgE is not utilized in many countries and experience in the literature is limited. In Denmark, tests for specific IgE to penicillins have been used routinely for many years in penicillin allergy

investigation. Danish guidelines from 2006 recommended measuring specific IgE in all patients referred for penicillin allergy investigation. Guidelines were updated in 2019 and current recommendations are to only measure specific IgE to penicillins in patients with immediate type reactions. Elevated specific IgE to one or more penicillins is considered diagnostic in the context of a clear history of an immediate type reaction. Thus, patients with immediate type reactions will only proceed to skin testing and a titrated drug provocation test if specific IgE towards penicillins are negative (<0.35 kUA/L).

The specific IgE assays available in the Allergy Clinic in Gentofte Hospital are penicillin V/phenoxyethylpenicillin (PV), penicillin G/benzylpenicillin (PG), amoxicillin (AMX) and ampicillin (AMP). In addition, the department has routinely performed specific IgE to penicillin minor determinants (MD). The ImmunoCAP Penicillin MD test was developed using

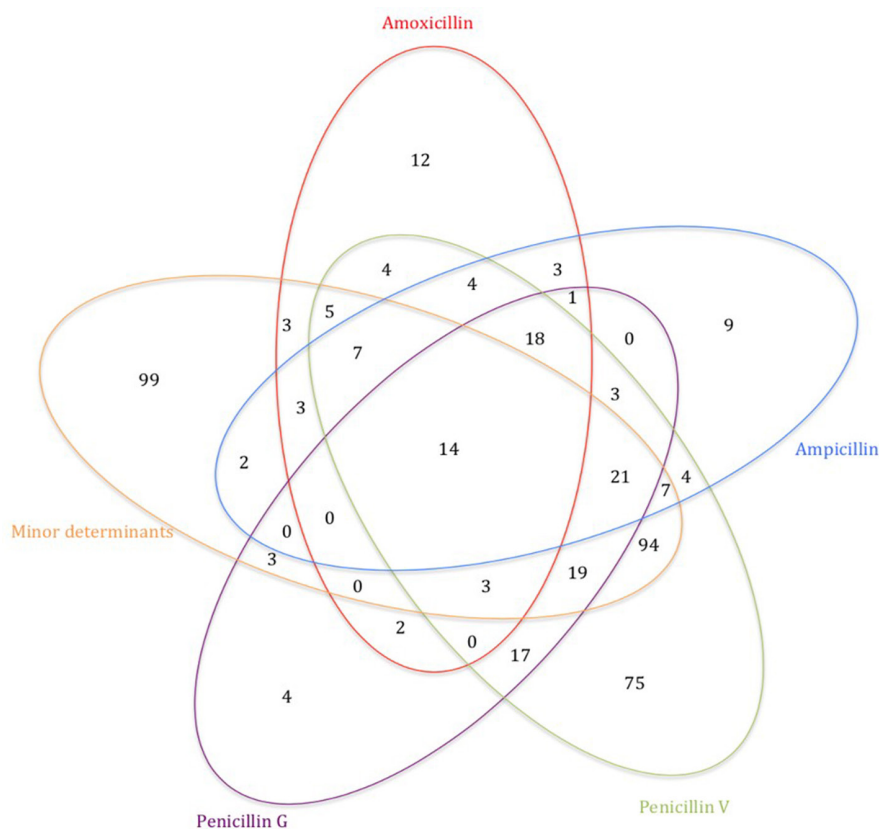


FIGURE 1 Venn-diagram of patients with elevated specific IgE to penicillins ($n=436$).

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Penicillin V and designed to keep the bicyclic beta lactam-thiazolidine structure intact and hence, measuring specific IgE to minor epitopes. The MD specific IgE assay was initially available to the clinic on a research basis but is now commercially available in some countries. All assays are using the ImmunoCAP technology (ThermoFisher Scientific).

In this study, we aimed to identify the proportion of patients with suspected penicillin allergy where specific IgE to penicillins is elevated and to evaluate if patients with elevated specific IgE to minor determinants differ clinically from patients with elevated specific IgE to one or more other penicillins.

TABLE 1 Characteristics of patients with elevated specific IgE to penicillins.

	Patients mono-sensitized to specific IgE MD (<i>n</i> = 97 ^a)	Patients with elevated specific IgE to one or more other penicillins (<i>n</i> = 333 ^b)	<i>p</i> -Value
Age			
<18 years	2 (2.1%)	10 (3.0%)	1 ^c
18–65 years	61 (62.9%)	237 (71.3%)	
>65 years	34 (35.1%)	86 (25.9%)	.985
Sex			
Male	31 (32.0%)	104 (31.3%)	.818
Female	66 (68.0%)	229 (68.7%)	
Reaction type			
Immediate reaction (<2h)	30 (30.9%)	109 (32.8%)	.200
Non-immediate reaction or unknown	67 (69.1%)	224 (67.2%)	
Symptoms			
Urticaria	31 (32.0%)	116 (34.9%)	.506
Angioedema	23 (23.7%)	93 (28.0%)	.318
Pruritus	69 (71.1%)	151 (45.5%)	.673
Other or unknown rash	42 (43.3%)	179 (53.9%)	.436
Respiratory symptoms	14 (14.4%)	72 (21.7%)	.414
Circulatory symptoms	7 (7.2%)	47 (14.2%)	.261
Treatment			
Antihistamine	80 (82.5%)	182 (54.8%)	.076
Steroid	35 (36.1%)	120 (36.1%)	.515
Adrenaline	7 (7.2%)	33 (10.0%)	.248

Note: Comparison between patients with elevated specific IgE to MD only and patients with elevated specific IgE to one or more of the other penicillins (penicillin G, penicillin V, amoxicillin and ampicillin).

^a2 patients were excluded due to missing data.

^b4 patients were excluded due to missing data.

^cFisher Exact Test.

Key points

- Specific IgE to penicillins have been recommended in the context of immediate-type allergic reactions.
- Specific IgE penicillin minor determinants identify additional sensitizations compared to other specific IgE penicillin assays.
- Specific IgE penicillin minor determinants should be considered in immediate-type reactions although validation is lacking.

Approval to retrieve data with exemption from informed patient consent was obtained from The Danish Patient Safety Authority journal no. 31-1521-457. Specific IgE results from 9100 patients referred to The Allergy Clinic at Gentofte Hospital between 2010 and 2020 were retrieved from the biobank at the Laboratory of Medical Allergology. In total 477 patients (5.2%) had elevated specific IgE to at least one penicillin. Clinical data on patients with an elevated specific IgE to one or more of the five penicillins were collected from the medical notes of the regional electronic patient journal system. 436 patients had a relevant clinical history with a suspected allergic reaction to a penicillin and were included in the study. Due to waiting times for allergy investigation most patients started allergy investigation 6 to 12 months after index reaction. Patients were divided in two groups: (1) Patients with elevated specific IgE only to minor determinants (*n* = 99) and (2) Patients with elevated specific IgE to one or more of the other four penicillins (*n* = 337).

The groups were compared using chi-squared test and Fisher's exact test where appropriate (*n* < 10). All analyses were performed in R version 4.1.0 and *p*-values less than .05 were considered statistically significant.

The distribution of elevated specific IgE tests to the individual penicillins are shown in Figure 1. Of the 436 patients with elevated specific IgE, the majority had elevated specific IgE to PV 295 (67.7%) and MD 280 (64.2%), with fewer positive tests for PG 105 (24.1%), AMX 79 (18.1%) and AMP 96 (22.0%). A total of 99 patients (22.7%) were mono-sensitized to MD, 75 (17.2%) mono-sensitized to PV, 4 (0.9%) to PG, 12 (2.8%) to AMX and 9 (2.1%) to AMP.

Table 1 shows the demographic and clinical characteristics of patients with elevated specific IgE to MD only, compared to patients with elevated specific IgE to one or more of the other four penicillins. No statistically significant differences were found between the two groups. Our study shows that compared to the four commonly used specific IgE assays for penicillins specific IgE MD was positive in a further 29.4% of patients with suspicion of penicillin hypersensitivity, which might increase the sensitivity of penicillin sIgE testing. The characteristics of patients identified by the specific IgE MD assay did not differ from those identified by the other assays. For patients with immediate type reactions to penicillins the specific IgE MD assay may therefore be an important supplement to existing tests, as elevated specific IgE or positive skin testing, in combination with a positive case

history, has previously been shown to be predictors of a clinically significant allergy.^{3,4} As IgE sensitization does not always correspond to clinical allergy, IgE levels should only be interpreted in the context of a relevant clinical history with an immediate type reaction, and thereby improving specificity. It has been suggested that in patients with very severe immediate type reactions, elevated specific IgE to one or more penicillins may be considered diagnostic, avoiding the need for confirmatory tests such as skin testing or drug provocation which may induce systemic reactions.^{1,5}

No other studies evaluating the specific IgE MD assay could be identified in the literature. However, several studies discuss penicillin minor determinants in skin testing and argue that skin tests with minor determinants are essential in evaluating suspected penicillin allergy as the two Penicillin V metabolites, penicilloate and penilloate, are important factors in inducing allergic responses.^{6,7} Other studies suggest that minor determinants derived from amoxicillin does not perform better than skin test with AMX or PG alone.^{8,9}

Findings in our study are not validated by skin testing or drug provocation testing which is a limitation as this means that sensitivity and specificity cannot be assessed. Also, 2/3 of patients with positive IgE have reported non-immediate or unknown reactions potentially further compromising specificity. However, the previously reported low sensitivity of specific IgE might improve when adding a specific IgE MD, as there is no difference between patients positive only to this assay and the other four penicillin IgE assays. Future studies should focus on identifying clear criteria for which cohorts of patients are likely to benefit from specific IgE tests as part of penicillin allergy investigations and specific IgE MD should be included. Specific IgE to penicillins are safer and more convenient for the patient than skin testing or the gold standard test of drug provocation. Establishing a role for specific IgE testing, especially in patients with severe immediate hypersensitivity, would improve patient management and the safety of allergy investigations.

AUTHOR CONTRIBUTIONS

VL, LHG, HM and SF took initiative to the article with regards to the conception and design. VL and NK acquired the data. VL, SF and JBB analysed the data. VL drafted the first draft. LHG, HM, JBB, LHB and LKP helped with interpretation of data. All authors have provided critical comments on the intellectual content of the article. All authors have approved the final version.

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KEYWORDS

anaphylaxis, drug allergy, drug hypersensitivity, immediate type hypersensitivity, penicillin, penicillin allergy, penicillin minor determinants, specific IgE, specific IgE to penicillins

CONFLICT OF INTEREST STATEMENT

VL, SF, HM, JBB, NK, LKP, LHB, LHG all declare that they have no conflicts of interest relevant to the content of this publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

- Romano A, Atanaskovic-Markovic M, Barbaud A, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams – an EAACI position paper. *J Allergy Clin Immunol.* 2020;75(6):1300-1315.
- Sousa-Pinto B, Tarrio I, Blumenthal KG, et al. Accuracy of penicillin allergy diagnostic tests: a systematic review and meta-analysis. *J Allergy Clin Immunol.* 2020;147(1):296-308.
- Tannert LK, Mortz CG, Skov PS, Bindslev-Jensen C. Positive skin test or specific IgE to penicillin does not reliably predict penicillin allergy. *J Allergy Clin Immunol.* 2017;5(3):676-683.
- van der Poorten MLM, van Gasse AL, Hagendorens MM, et al. Serum specific IgE antibodies in immediate drug hypersensitivity. *Clin Chim Acta.* 2020;504:119-124.
- Wöhl S, Ostermayer C, Sesztak-Greinecker G, Jarisch R, Hemmer W, Wantke F. Drug-specific history, skin and in vitro tests can reduce the need for drug provocation tests in betalactam-hypersensitivity. *Allergol Int.* 2021;70(2):244-251.
- Adkinson NF, Mendelson LM, Ressler C, Keogh JC. Penicillin minor determinants History and relevance for current diagnosis. *Ann Allergy Asthma Immunol.* 2018;121:537-544.
- Geng B, Eastman JJ, Mori K, Braskett M, Riedl AM. Utility of minor determinants in penicillin allergy skin testing. *Ann Allergy Asthma Immunol.* 2017;119:258-261.

8. Torres MJ, Ariza A, Fernández J, et al. Role of minor determinants of amoxicillin in the diagnosis of immediate allergic reactions to amoxicillin. *Allergy: European. J Allergy Clin Immunol.* 2010;65(5):590-596.
9. Rosenfield L, Kalicinsky C, Warrington R. A retrospective comparison of false negative skin test rates in penicillin allergy, using pencilloyl-poly-lysine and minor determinants or Penicillin G, followed by open challenge. *Allergy Asthma Clin Immunol.* 2015;11(1):1-6.