

Prevalence of self-reported and confirmed penicillin allergy in a Belgian outpatient population

To the editor,

β -lactam antibiotics (β -LABs), especially penicillins, are one of the predominant causes of drug hypersensitivity reactions (DHRs) with significant morbidity and mortality. Alternatively, unverified and spurious “penicillin allergy” has developed into a scourge with important medical and financial consequences for both the patient and society. According to the literature, 10%-20% of the population reports a “penicillin allergy” that was never accurately documented.¹ Most reports describe an unknown reaction or a poorly defined rash.²

However, over 90% of the individuals with a “penicillin allergy” tolerate the alleged culprit(s) during controlled drug challenges (DC) and are at unnecessary risk for suboptimal second-line antibiotic treatments.¹ Actually, “penicillin allergy” is associated with poorer outcomes, prolonged hospitalizations, readmissions, increased rates of *Clostridium difficile* and antimicrobial resistance, for example vancomycin.³

An important reason for penicillin (and other β -LABs) allergy to be overestimated is the fact that it is often a self-reported condition without any diagnostic verification together with an insufficient knowledge of cross-reactivity between penicillins and other B-LABs, mainly cephalosporins.⁴⁻⁶

In Belgium, data about the prevalence and consequences of a “penicillin allergy” are lacking. Hence, the aim of this study was to determine how many individuals, attending the outpatients' clinics of Allergology and Pediatric Allergology of the Antwerp University Hospital, claim to have a “penicillin allergy” and to identify the patients with a β -LAB allergy.

In this prospective observational study, participants were included via the outpatients' clinics of Allergology and Pediatric of the Antwerp University Hospital between September 2018 and August 2019.

They were asked the following binary question: “Do you (possibly) have a penicillin allergy?” Participants who responded “yes” were offered confirmatory testing,⁷ including quantification of total and specific IgE antibodies (FEIA ImmunoCAP, Phadia Thermo Fisher, Uppsala, Sweden) to penicillin G, penicillin V, ampicillin and amoxicillin, followed by skin prick testing (SPT) and when negative additional intradermal tests (IDT), including delayed readings after 48-72 hours, with penicillin G and amoxicillin and/or amoxicillin/clavulanic acid (AX/CL) according to the

suspected culprit of the index reaction (for the protocol of skin testing, see Table S1 in this article's Online Repository). Patients with negative skin testing and sIgE results were offered an oral DC with amoxicillin or AX/CL, as described elsewhere.⁸ A DC was considered positive when objective symptoms could be observed.

The local ethics committee approved this study (B300201524055), and patients or their representatives provided informed consent in accordance with the Declaration of Helsinki.

A total of 1,498 participants (769 female; 740 children) with a median age of 18 years (range 3 months-93 years) were included. As displayed in Figure 1, 169 participants (12%) claimed to have a “penicillin allergy” that was, except in one patient, never thoroughly investigated. Table S2 in this article's Online Repository shows the characteristics of the participants with a self-reported “penicillin allergy.” Women ($n = 106$) reported “penicillin allergy” significantly more frequent than men ($n = 63$) (14% vs 9%, χ^2 $P = .002$). A total of 45 participants (27%) described an index reaction to a “penicillin” during childhood. The most frequent clinical presentation was an undefined “rash” ($n = 63$; 37%). In 56 participants (33%), the self-reported “penicillin allergy” was the reason for referral to our outpatient's clinic. In the other participants, their “penicillin allergy” was identified as a secondary problem.

A total of 120 participants with a self-reported penicillin allergy agreed to have additional testing as mentioned before. In 49 participants, no further investigations were planned because either the participant rejected the study because he considered the “penicillin allergy” to lack sufficient priority ($n = 45$) or the allergist decided, based on a thorough history, that the index reaction was not compatible with a DHR ($n = 4$). These 4 participants were considered as delabelled.

Of these 120 participants, 95 completed the diagnostic work-up. As shown in Table 1, 9/95 (9%) patients demonstrated a natural and semi-synthetic penicillin or amoxicillin and/or AX/CL hypersensitivity. In 7 patients, a diagnosis of an immediate-type hypersensitivity reaction (IDHR) was established, whereas in the remaining 2 patients a non-immediate-type hypersensitivity reaction (NIDHR) was demonstrable.

A total of 43 of the 86 participants with a negative DC could be queried about subsequent penicillin use. Three participants were uneventfully re-exposed to amoxicillin. The remaining 40 participants

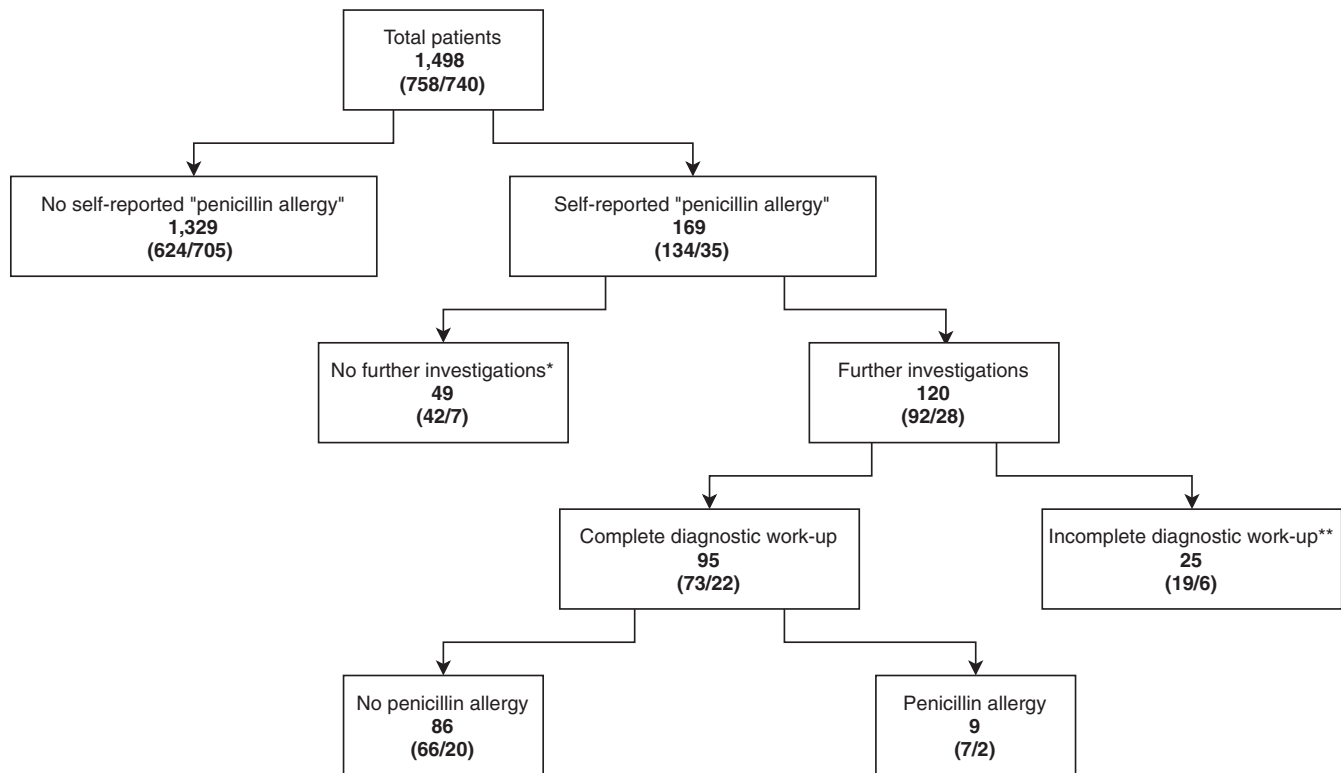


FIGURE 1 This flowchart gives an overview of the study population. The information in brackets displays the number of adults/children. *No further investigations were planned because either the patient considered the “penicillin allergy” to lack sufficient priority ($n = 45$) or the allergist decided, based on a thorough history, that the index reaction was not compatible with a DHR ($n = 4$). **Investigations had to be postponed for various reasons (eg, pregnancy and intake of antihistamines). In 2 out of these 25 participants, the DC resulted in only subjective symptoms (itch, epigastric pain, shortness of breath). As both were unwilling to repeat the DC, they were included in the group of the patients with incomplete diagnostic work-up.

had no indication for penicillin yet. Despite negative DC, 4/40 participants remained reluctant to take a penicillin ever again, in 1 out of 4 reinforced by other physicians.

To our knowledge, this is the largest study investigating the prevalence of self-reported penicillin allergy in a Belgian outpatient population. 12% of the individuals attending our outpatients' clinics claim to have a “penicillin allergy.” However, although delabelling programmes are strongly recommended, only in 33% of the participants evaluation of their self-reported “penicillin allergy” was the reason of the consultation. This means that in our country, the medical and financial burden of overdiagnosis of “penicillin allergy” is still not completely perceived. Paralleling observations by others, in most cases history of “penicillin allergy” is extremely vague. Clinical description is generally limited to an unspecified “rash” due to a “penicillin” without any further detail about the cutaneous lesions, associated extracutaneous symptoms, offender and timing. Every physician who witnesses a potential DHR should, upon referral to the allergist, provide a complete and correct description, to allow identification of the underlying pathophysiological mechanisms and orientation of confirmatory testing.

Furthermore, in line with others, we could safely delabel 91% of the participants with a “penicillin allergy” who had complete

diagnostic exploration. Efforts are needed to persuade larger numbers of participants to have their “penicillin allergy” confirmed or more likely infirm and to clarify that delabelling is only worthwhile if a person is willing to discard the erroneous suspicion. After all, almost 10% of the participants who were successfully delabelled by negative DC remained reluctant for any subsequent intake. Alternatively, in 9 cases a diagnosis of hypersensitivity towards natural and semi-synthetic penicillin, amoxicillin or amoxicillin/clavulanic acid was established. This indicates that an undefined rash should not necessarily represent an indication for direct DCs without prior skin tests.

The main limitation of this study is that results may not be extrapolated to the general population as in our study only participants visiting our outpatients' allergology clinics were included which may lead to an overestimation of self-reported “penicillin allergy.” Moreover, further diagnostic work-up was rejected or incomplete in 70 (41%) participants, which could also have influenced our data. A final limitation of this study is that clavulanic hypersensitivity was not ruled out in 4 patients with a positive skin test or drug challenge with AX/CL. In conclusion, self-reported “penicillin allergy” is common in those attending outpatient allergology clinics in our region and warrants confirmatory diagnostics to establish or discard diagnosis. Further efforts to optimize the diagnostic approach and to control the plague of alleged “penicillin allergy” are needed.

TABLE 1 Characteristics of patients with a genuine penicillin allergy: demographics, culprit, clinics, laboratory and skin test findings and outcomes of challenges

Patient	Sex	Age	Culprit (index)	Symptoms (index)	Time interval (months) ^d	sIgE FEIA ImmunoCAP (kUA/L)				Skin testing			Drug challenge			
						tIgE	PG	PV	Amp	AX	PG	AX/CL	AX	PG	AX/CL	AX
1	F	62	AX	Undefined rash, swelling, dyspnoea	12	53	<0.10	<0.10	NP	<0.10	Negative	NP	Positive	Negative	NP	NP
2 ^b	F	61	Unknown	Unknown	36	20	<0.10	<0.10	NP	<0.10	Negative	Positive	NP	NP	NP	NP
3 ^a	F	1	AX/CL	MPE	3	NP	NP	NP	NP	NP	Negative	Negative	NP	NP	Positive ^e	NP
4	F	41	Unknown	Undefined rash, swelling	NR	190	<0.10	<0.10	NP	<0.10	Negative	Negative	NP	NP	Positive ^f	NP
5	F	55	Unknown	Undefined rash, swelling	NR	487	<0.10	1.67	<0.10	0.23	Negative	Negative	NP	NP	NP	NP
6	F	52	Unknown	Undefined rash	NR	2751	0.11	0.19	0.16	0.21	Positive	NP	NP	NP	NP	NP
7 ^a	M	43	AX/CL	Undefined rash	3	32	<0.10	<0.10	<0.10	<0.10	Negative	Positive	Positive	Negative	NP	NP
8	F	26	AX	Urticaria, dyspnoea	4	151	1.55	0.60	0.56	0.43	Positive	NP	NP	NP	NP	NP
9 ^c	M	1	AX/CL	Undefined rash	4	7	<0.10	<0.10	<0.10	<0.10	Negative	Positive	NP	NP	NP	NP

Abbreviations: Amp, ampicillin; AX, amoxicillin; AX/CL, amoxicillin/clavulanic acid; F, female; FEIA, fluorescence enzyme immunoassay; M, male; MPE, maculopapular exanthema; NP, not performed; NR, not reported; PG, penicillin G; PV, penicillin V; sIgE, specific IgE; tIgE, total IgE.

^aDelayed type IV hypersensitivity reaction based on positive delayed reading intradermal test or positive drug challenge.

^bDiagnostic work-up, as shown in the table, was already performed in 2011 at our department. Skin testing with penicillin G, amoxicillin and amoxicillin/clavulanic acid was repeated during this study but turned negative (data not shown).

^cSkin testing with amoxicillin was not performed due to practical reasons.

^dTime between the index reaction and the start of our diagnostic work-up.

^eAn MPE starting 2 d after the drug challenge.

^fThe patient experienced anaphylaxis 30 min after the full dose. Skin testing was repeated and remained negative.

ACKNOWLEDGMENTS

DGE is Senior Clinical Researcher of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1800614N). ALVG is Fellow of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1113617N). VS is Senior Clinical Researcher of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1804518N). Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek Project (G069019N).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Athina L. Van Gasse^{1,2} 

Redouane Oulkadi¹

Zakaria Mousati¹

Didier G. Ebo¹ 

Anca M. Chiriac^{3,4}

Marie-Line M. Van Der Poorten^{1,2} 

Margo M. Hagendorens^{1,2} 

Margaretha A. Faber¹ 

Jessy Elst¹ 

Christel M. Mertens¹ 

Leander De Puyseleir¹ 

Samuel Coenen⁵ 

Vito Sabato¹ 

¹Faculty of Medicine and Health Sciences, Department of Immunology, Allergology, Rheumatology and Infla-Med Centre of Excellence, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium

²Faculty of Medicine and Health Sciences, Department of Paediatrics and the Infla-Med Centre of Excellence, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium

³Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France

⁴UMR-S 1136, INSERM-Sorbonne Université, Equipe EPAR-IPLESP, Paris, France

⁵Faculty of Medicine and Health Sciences, Vaccine & Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium

Correspondence

Didier G. Ebo, Immunology – Allergology – Rheumatology, Faculty of Medicine and Health Sciences, University of

Antwerp, Campus Drie Eiken T5.95, Universiteitsplein 1, 2610 Antwerpen, Belgium.

Email: immuno@uantwerpen.be

Athina L Van Gasse and Redouane Oulkadi authors have equally contributed to the manuscript.

ORCID

Athina L. Van Gasse  <https://orcid.org/0000-0002-3434-4333>

Didier G. Ebo  <https://orcid.org/0000-0003-0672-7529>

Marie-Line M. Van Der Poorten  <https://orcid.org/0000-0002-3043-3339>

Margo M. Hagendorens  <https://orcid.org/0000-0001-6361-9503>

Margaretha A. Faber  <https://orcid.org/0000-0002-1277-5052>

Jessy Elst  <https://orcid.org/0000-0003-3506-8200>

Christel M. Mertens  <https://orcid.org/0000-0003-2359-0771>

Leander De Puyseleir  <https://orcid.org/0000-0001-5281-5592>

Samuel Coenen  <https://orcid.org/0000-0002-1238-8052>

Vito Sabato  <https://orcid.org/0000-0002-1321-314X>

REFERENCES

1. Castells M, Khan DA, Phillips EJ. Penicillin allergy. *N Engl J Med*. 2019;381:2338-2351.
2. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA*. 2019;321:188-199.
3. 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;133:790-796.
4. Shah NS, Ridgway JP, Pettit N, Fahrenbach J, Robicsek A. Documenting Penicillin Allergy: The Impact of Inconsistency. *PLoS One*. 2016;11:e0150514.
5. Daulat S, Solensky R, Earl HS, Casey W, Gruchalla RS. Safety of cephalosporin administration to patients with histories of penicillin allergy. *J Allergy Clin Immunol*. 2004;113:1220-1222.
6. Jeffres MN, Narayanan PP, Shuster JE, Schramm GE. Consequences of avoiding beta-lactams in patients with beta-lactam allergies. *J Allergy Clin Immunol*. 2016;137:1148-1153.
7. Romano A, Atanaskovic-Markovic M, Barbaud A, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams - an EAACI position paper. *Allergy*. 2019. <https://doi.org/10.1111/all.14122>. [Epub ahead of print].
8. Van Gasse AL, Ebo DG, Chiriac AM, et al. The limited value of prolonged drug challenges in nonimmediate amoxicillin (clavulanic acid) hypersensitivity. *J Allergy Clin Immunol Pract*. 2019;7(7):2225-2229.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Online repository

Table S1. Protocol for skin testing

A) Benzylpenicillin

	Concentration
Skin prick test	10 IU/mL
	1000 IU/mL
	100 000 IU/mL
Intradermal test	10 IU/mL
	1000 IU/mL
	100 000 IU/mL

B) Amoxicillin or amoxicillin clavulanic acid

	Concentration
Skin prick test	0.2 mg/mL
	2 mg/mL
	20 mg/mL
Intradermal test	0.2 mg/mL
	2 mg/mL
	20 mg/mL

Histamine 10 mg/mL (ALKAbello, Hørsholm, Denmark) and isotonic sodium chloride were used as positive and negative controls respectively.

Skin prick tests were read after 15 minutes and considered positive when the wheal of the wheal and flare reaction exceeded 3 mm. Patients with negative skin prick test had additional intradermal test. Intradermal test responses were considered positive when the wheal of the wheal and flare reaction equalled or exceeded 5 mm.

Table S2: Characteristics of patients with a self-reported penicillin allergy

Characteristic	Value
Age (children/adults)	35/134
Sex (M/F)	63/106
Drug index reaction n (%)	
AX	28 (17)
AX/CL	29 (17)
AmP	1 (1)
Missing data	111 (66)
Age index reaction, n (%)	
Adult	26 (15)
Child	45 (27)
Missing data	98 (58)
Symptoms index reaction as described by the patient, n (%)	
Undefined rash with systemic manifestations ¹	10 (6)
Undefined rash without systemic manifestations suggestive for type I DHR	53 (31)
Urticaria and/or AO with systemic manifestations suggestive for type I DHR ²	4 (2)
Urticaria and/or AO without systemic manifestations	21 (12)
Maculopapular exanthema	5 (3)
Others ³	13 (8)
Missing data	63 (37)
Delay symptoms, n (%)	
During antibiotic treatment	
<i>After the first dose</i>	23 (14)
<i>Other</i>	27 (16)
After the antibiotic treatment was stopped	3 (2)
Missing data	116 (69)

AmP, ampicillin; AX, amoxicillin; AX/CL, amoxicillin/clavulanic acid; DHR, drug hypersensitivity reaction; F, female; M, men y, years; AO, angioedema

¹ dyspnoea, hypotension, vomiting

² vomiting, diarrhoea

³ dyspnoea, vomiting, dizziness, itch