This item is the archived peer-reviewed author-version of:

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

Reference:
Van Gasse Athina, Oulkadi Redouane, Mousati Zakaria, Ebo Didier, Chiriac Anca M., van der Poorten Marie-Line, Hagendorens Margo, Faber Margaretha, Elst Jessy, Mertens Christel, .... Prevalence of self-reported and confirmed penicillin allergy in a Belgian outpatient population
Allergy: European journal of allergy and clinical immunology - ISSN 0105-4538 - Hoboken, Wiley, 75:8(2020), all.14292
Full text (Publisher's DOI): https://doi.org/10.1111/ALL.14292
To cite this reference: https://hdl.handle.net/10067/1694950151162165141
Prevalence of self-reported and confirmed penicillin allergy in a Belgian outpatient population

Athina L Van Gasse MD, Redouane Oulkadi BaSc, Zakaria Mousati BaSc, Didier G Ebo MD, PhD, Anca M Chiriac MD, PhD, Marie-Line M Van Der Poorten MD, Margo M Hagendorens MD, PhD, Margaretha A Faber MD, PhD, Jessy Elst MSc, Christel M Mertens MLT, Leander De Puysseleyr MD, Samuel Coenen MD, PhD, Vito Sabato MD, PhD

1 Faculty 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)

2 Faculty of Medicine and Health Sciences, Department of Paediatrics, University of Antwerp, and Antwerp University Hospital, Antwerp (Belgium)

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

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

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

* Both authors have equally contributed to the manuscript

Running title: Prevalence of penicillin allergy in a Belgian population

Correspondence:
D. Ebo MD PhD
University of Antwerp
Faculty of Medicine and Health Sciences
Immunology – Allergology - Rheumatology
Campus Drie Eiken T5.95
Universiteitsplein 1
2610 Antwerpen
Belgium
Tel: ++ 32 (0) 3 2652595
immuno@uantwerpen.be

The authors declare no conflict of interest.
ORCID ID

Van Gasse Athina: 0000-0002-3434-4333
Ebo Didier: 0000-0003-0672-7529
Van Der Poorten Marie-Line: 0000-0002-3043-3339
Hagendorens Margo: 0000-0001-6361-9503
Faber Margaretha: 0000-0002-1277-5052
Elst Jessy: 0000-0003-3506-8200
Mertens Christel: 0000-0003-2359-0771
De Puysseleyr Leander: 0000-0001-5281-5592
Coenen Samuel: 0000-0002-1238-8052
Sabato Vito: 0000-0002-1321-314X
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. Most reports describe an unknown reaction or a poorly defined rash.

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. Actually, “penicillin allergy” is associated with poorer outcomes, prolonged hospitalizations, readmissions, increased rates of Clostridium difficile and antimicrobial resistance, e.g. vancomycin.

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 β-LABs, mainly cephalosporins.

In Belgium, data about the prevalence and consequences of a “penicillin allergy” are lacking. Hence, the aim of this study is 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, including quantification of total and specific (s)IgE antibodies (FEIA ImmunoCAP, Phadia ThermoFisher, 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 E1 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. 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.

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 E2 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%, χ² P = 0.002). 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.

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.

95 out of these 120 participants 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 remainder 2 patients a nonimmediate type hypersensitivity reaction (NIDHR) was demonstrable.

43 of the 86 participants with a negative DC, could be queried about subsequent penicillin use. 3 participants were uneventfully re-exposed to amoxicillin. The remaining 40 participants 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 programs 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.

Athina L Van Gasse MD, Redouane Oulkadi BaSc, Zakaria Mousati BaSc, Didier G Ebo MD, PhD
Anca M Chiriac MD, PhD4,5
Marie-Line M Van Der Poorten MD1,2
Margo M Hagendorens MD, PhD1,2
Margaretha A Faber MD, PhD1
Jessy Elst MSc1
Christel M Mertens MLT1
Leander De Puysseleyr MD1
Samuel Coenen MD, PhD3
Vito Sabato MD, PhD1

From the 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) and the 2Faculty of Medicine and Health Sciences, Department of Paediatrics, University of Antwerp, and Antwerp University Hospital, Antwerp (Belgium) and the 3Faculty of Medicine and Health Sciences, Vaccine & Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp (Belgium) and the 4Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France and the 5UMR-S 1136 INSERM-Sorbonne Université, Equipe EPAR - IPLESP, Paris, France. * Both authors have equally contributed to the manuscript

Acknowledgements

DGE is a Senior Clinical Researcher of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1800614N). ALVG is a fellow of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1113617N). VS is a Senior Clinical Researcher of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1804518N). Foundation Flanders/Fonds Wetenschappelijk Onderzoek Project (G069019N).
Figure 1: Composition of the study population.

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 (e.g. pregnancy, 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.
Table 1: Characteristics of patients with a genuine penicillin allergy: demographics, culprit, clinics, laboratory and skin test findings and outcomes of challenges.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Culprit (index)</th>
<th>Symptoms (index)</th>
<th>Time interval (months)</th>
<th>tlgE</th>
<th>sigE FEIA ImmunoCAP (kUA/L)</th>
<th>Skin testing</th>
<th>Drug challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PG</td>
<td></td>
<td></td>
<td></td>
<td>PG, PV, Amp, AX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>62</td>
<td>AX</td>
<td>Undefined rash, swelling, dyspnoea</td>
<td>12</td>
<td>53</td>
<td>&lt;0.10, &lt;0.10, NP, &lt;0.10</td>
<td>Negative, NP</td>
<td>Positive, Negative, NP</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>61</td>
<td>Unknown</td>
<td>Unknown</td>
<td>36</td>
<td>20</td>
<td>&lt;0.10, &lt;0.10, NP, &lt;0.10</td>
<td>Negative, Positive</td>
<td>NP, NP, NP</td>
</tr>
<tr>
<td>3†</td>
<td>F</td>
<td>1</td>
<td>AX/CL</td>
<td>MPE</td>
<td>3</td>
<td>NP</td>
<td>NP, NP, NP, NP, NP</td>
<td>Negative, Negative, NP</td>
<td>NP, NP, NP</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>41</td>
<td>Unknown</td>
<td>Undefined rash, swelling</td>
<td>NR</td>
<td>190</td>
<td>&lt;0.10, &lt;0.10, NP, &lt;0.10</td>
<td>Negative, Negative, NP</td>
<td>NP, Positive, NP</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>55</td>
<td>Unknown</td>
<td>Undefined rash, swelling</td>
<td>NR</td>
<td>487</td>
<td>&lt;0.10, 1.67, &lt;0.10, 0.23</td>
<td>Negative, Negative, NP</td>
<td>NP, NP, NP</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>52</td>
<td>Unknown</td>
<td>Undefined rash</td>
<td>NR</td>
<td>2751</td>
<td>0.11, 0.19, 0.16, 0.21</td>
<td>Positive, NP</td>
<td>NP, NP, NP</td>
</tr>
<tr>
<td>7†</td>
<td>M</td>
<td>43</td>
<td>AX/CL</td>
<td>Undefined rash</td>
<td>3</td>
<td>32</td>
<td>&lt;0.10, &lt;0.10, &lt;0.10, &lt;0.10</td>
<td>Negative, Positive, Positive, Negative</td>
<td>NP, NP, NP</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>26</td>
<td>AX</td>
<td>Urticaria, dyspnoea</td>
<td>4</td>
<td>151</td>
<td>1.55, 0.60, 0.56, 0.43</td>
<td>Positive, NP</td>
<td>NP, NP, NP</td>
</tr>
<tr>
<td>9†</td>
<td>M</td>
<td>1</td>
<td>AX/CL</td>
<td>Undefined rash</td>
<td>4</td>
<td>7</td>
<td>&lt;0.10, &lt;0.10, &lt;0.10, &lt;0.10</td>
<td>Negative, Positive, NP</td>
<td>NP, NP, NP</td>
</tr>
</tbody>
</table>

AX/CL, amoxicillin clavulanic acid; AX, amoxicillin; MPE, maculopapular exanthema; PG, penicillin G; PV, penicillin V; Amp, ampicillin; NP, not performed; NR, not reported; M, male; F, female; FEIA, fluorescence enzyme immunoassay

1 Delayed type IV hypersensitivity reaction based on positive delayed reading intradermal test or positive drug challenge.
2 Diagnostic 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).
3 Skin testing with amoxicillin was not performed due to practical reasons.
Time between the index reaction and the start of our diagnostic work-up
An MPE starting 2 days after the drug challenge
The patient experienced anaphylaxis 30 minutes after the full-dose. Skin testing was repeated and remained negative.
References