

Safe De-Labeling of Patients at Low Risk of Penicillin Allergy in Denmark

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Keywords

Penicillin allergy · De-labeling · Prolonged drug provocation · Risk stratification · Challenge test

Abstract

Introduction: Penicillin allergy is suspected in 10% of hospital inpatients but can be disproved in 90% of cases. Direct oral provocation without preceding tests among low-risk patients has proven to be safe in studies of both children and adults and is gaining use across the world. The aims of this study were to investigate the rate of severe allergic reactions to direct oral drug provocation, without preceding tests, in penicillin allergy patients stratified to be at low risk, as well as to examine if these patients have barriers to penicillin allergy de-labeling and future use of penicillins. **Methods:** Adult patients referred to a university hospital allergy clinic with a suspected penicillin allergy were prospectively risk evaluated. Patients stratified to be at low risk were offered a direct oral provocation with a single-dose amoxicillin followed by 4 days of continued treatment. The same risk stratification criteria were applied to a larger retrospective

cohort. **Results:** In the prospective study population, 202 patients had a direct oral drug provocation and 20 (10%) were positive. There were no cases of anaphylaxis or severe delayed hypersensitivity. Fifteen reactions were benign rashes with onset >1 day after initial dosing, and 13 of these were maculopapular rashes. The same low-risk criteria were applied retrospectively to patients in a drug provocation database, and 1,759 patients fulfilled the criteria; of these, 10% had positive provocations, and there were no cases of anaphylaxis or severe delayed hypersensitivity. De-labeled patients in the prospective study reported not to fear future penicillin intake, after prolonged provocation. **Conclusion:** The risk stratification criteria for identifying low-risk patients for the oral drug provocation test without prior skin testing were safe in terms of avoiding anaphylaxis or severe delayed hypersensitivity. Benign delayed skin reactions still occurred, and access to allergy advice and follow-up is necessary.

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Introduction

Antibiotic resistance has been nominated by the WHO to be one of the largest threats to global health [1]. There is an increased focus on strategies to reduce antibiotic resistance both politically and in the health care systems through antibiotic stewardships [1–3]. Penicillin allergy is suspected in 10% of hospital inpatients, but studies have shown that in up to 90% of patients, allergy cannot be confirmed on allergy investigation, and the allergy label can be removed (de-labeling) [4–18]. Incorrect labeling fuels antibiotic resistance as patients with a penicillin allergy label receive alternative broad-spectrum antibiotics, which are often less effective [19–22], more costly [20–23], and directly contribute to antibiotic resistance [11, 20]. In addition, patients with a penicillin allergy label are hospitalized longer [11, 20, 23, 24] and have a higher rate of adverse effects including infection with multiresistant bacteria [11, 20, 23, 25] which leads to increased morbidity [26, 27] and health care costs [20, 23, 24].

The concept of risk evaluation/stratification and direct oral provocation in adults has been proven to be safe in published studies and is gaining increasing use across the world, especially in the USA, UK, Australia, and New Zealand, but the suggested risk stratification and method for de-labeling differ [6, 16, 28–33]. So far, only few guidelines [34–36] include the use of risk stratification and recommendations to tailor allergy investigations to the risk of a reaction. The gold standard of drug allergy investigation is drug provocation (re-exposing the patient to the drug under relevant observation). In many countries, more time-consuming and extensive/expensive investigations with initial skin testing are recommended even for low-risk patients, and drug provocation is only offered if all other tests are negative [34, 37–40]. In recent Danish guidelines, it is suggested that all patients should be risk stratified and that patients assessed to have a low risk of penicillin allergy are investigated with a direct oral provocation, without preceding skin or blood tests [35, 36].

In addition, limited knowledge is available on whether patients have confidence in the results of allergy investigations. Studies have shown that some patients will not take the incriminated drug again, even after a negative drug allergy testing [41–44].

Following the launch of the updated Danish guidelines in 2019, an investigation procedure with direct oral challenge for patients with a low risk of penicillin allergy was introduced in our clinic to optimize use of resources. To evaluate the risk of a reaction during

penicillin allergy testing, risk stratification criteria, inspired by the recommendations from the guidelines, were developed. The aims of the present study were as follows:

- (i) To investigate the rate of severe allergic reactions when using a direct oral drug provocation, without preceding tests, in low-risk penicillin allergy patients in a Danish population.
- (ii) To examine if patients at a low risk of penicillin allergy have barriers to penicillin allergy de-labeling and future use of penicillins after de-labeling.

Materials and Methods

The study included a prospective and a retrospective study population and took place at the Allergy clinic, Herlev and Gentofte Hospital, Denmark. It is the only tertiary referral center for adult patients with suspected drug allergy in an area with 1.8 million inhabitants, receiving about 150 drug allergy referrals per month, from both primary care and hospital departments.

Study Approvals

The prospective study protocol was reviewed and approved by the Hospital Administration at Herlev and Gentofte Hospital, Hellerup, Denmark (Workzone No. 9075674), and written informed consent was obtained from patients. The retrospective study was performed under the existing database and project approval from the Regional Centre for Research Approvals (Jr.nr. P-2019-390), which includes exemption from written informed consent from patients. Under the Danish law, ethical approval was not required for neither the prospective nor the retrospective study.

Prospective Study Population

From May 2019 to October 2020, consecutive adult patients referred for penicillin allergy testing were screened for low-risk criteria. Patients evaluated to be at low risk of penicillin allergy were offered investigation with a direct oral challenge.

Risk Evaluation

Risk evaluation was performed by applying the risk stratification criteria, based on the clinical history. Patients were risk classified to high risk, low risk, or penicillin allergy unlikely (i.e., same risk as background population), see Table 1. Only patients stratified to low risk were included in the study. To improve characterization of skin symptoms, pictures of urticaria and maculopapular exanthemas (MPEs) were shown to the patient. Skin symptoms were considered MPE if the patient identified the rash as shown on the picture or described it as “macular/papular” or measles- or rubella-like.

Inclusion Criteria for Prospective Study

- Patients ≥ 18 years of age referred with a suspected allergy to penicillin G, penicillin V, aminopenicillins (pivampicillin, ampicillin, amoxicillin, and amoxicillin/clavulanic acid), or unknown penicillin.
- Low-risk history of penicillin allergy (Table 1).

- Exclusion Criteria for Cohort
- Suspected allergy to penicillins not mentioned above or other drugs/antibiotics.
- Penicillin allergy unlikely (Table 1).
- High-risk history of penicillin allergy (Table 1).
- Severe comorbidities such as COPD, severe asthma, ischemic heart disease, and heart failure.
- Pregnancy or breastfeeding.
- Specific IgE levels for penicillins above 0.35 kUA/L (if measured).

Specific IgE to Penicillins

The updated Danish guidelines on the investigation of penicillin allergy from 2019 only recommend specific IgE testing for patients with immediate-type reactions. However, previous Danish guidelines recommended that penicillin specific IgE testing should be performed by general practitioners (GPs) in all patients before referral for penicillin allergy investigation. Most GPs therefore still order sIgEs to all penicillins, or a combination of penicillin V, penicillin G, amoxicillin, and ampicillin in most patients.

Drug Provocation Test

The drug provocation tests were performed with one oral full-dose amoxicillin 500 mg in all patients. Blood pressure, pulse, and peak flow were measured before provocation. Immediate reactions (IR) were defined as reactions developing within 2 h of the first dose, and delayed reactions were reactions that developed later than 2 h after the first dose. If no reaction occurred after 2-h observation, the patient continued the provocation the next day at home by taking amoxicillin 500 mg $\times$ 2 daily for the following 4 days (prolonged provocation).

If a reaction occurred at home, the patient was instructed to contact the department (during office hours) or the emergency department (outside of office hours) for further guidance and treatment. Patients were issued with antihistamines and oral steroids for treatment of allergic symptoms. Follow-up was performed 1 to 4 weeks later, to secure outcome and for completion of the questionnaire. If no reaction had occurred, the patient was informed about tolerating penicillin and the removal of the penicillin allergy label from hospital medical charts.

Patient Questionnaire

The questionnaire was divided into two parts: a pre-provocation questionnaire and a post-provocation questionnaire, answered before and after the prolonged provocation. Questions in pre- and post-provocation questionnaires were comparable. The first question concerned how certain the patient was about having penicillin allergy (answers in a Likert scale from 0 to 10). The second question was whether the patient would take penicillin if it had been prescribed by a doctor (outside of an allergy clinic setting), and the third question was about how safe the patient would feel about taking penicillins again, if allergy testing was negative (answers in a Likert scale from 0 to 10). The fourth question was only asked after drug provocation and concerned compliance with completing the full course of penicillin during prolonged provocation. Only patients who understood Danish participated in the questionnaire part of the study. Responses from patients who developed a reaction during DPT or for other reasons did not answer the post-provocation questionnaire were excluded from the questionnaire analysis. Translated questionnaire is in online supplementary Material (see www.karger.com/doi/10.1159/000521708).

Table 1. Risk stratification criteria modified from Danish guidelines on the investigation of penicillin allergy from 2019 [35, 36]

High risk	Low risk	Penicillin allergy unlikely
>1 allergic reaction to suspected culprit drug Onset of symptoms <2 h after first dose Shortness of breath or globus sensation Syncope or hypotension Urticaria/intense pruritus Nonbenign skin symptoms defined as mucosal affection, blistering, desquamation, angioedema, maculopapular skin exanthema lasting for 7 days or more Eosinophilia Suspicion of serum sickness disease Treatment with oral steroids or adrenaline	Single suspected allergic reaction Onset of symptoms >2 h after first dose Benign skin symptoms defined as uncharacterized exanthema, flushing, light pruritus, or/and maculopapular exanthema lasting <7 days or Unknown/sparse information about index reaction (most often unspecific rash as a child with no precise information about symptoms, timing, treatment)	Only mild nonallergic symptoms, e.g., headache, gastrointestinal symptoms No personal history of an allergic reaction (i.e., only family history of suspected penicillin allergy)

Table 2. Demographics and data about the index reaction for the prospective study population (*n* = 202)

	Allergic (<i>n</i> = 20)	De-labeled (<i>n</i> = 182)	Total (<i>n</i> = 202)
Female, <i>n</i> (%)	16 (80)	118 (65)	134 (66)
Age, median (IQR), years	45 (31–60)	50 (39–63)	50 (38–62)
Years between index reaction and DPT, median (IQR)	31 (22–38)	39 (26–48)	38 (24–47)
Age group at time of index reaction, <i>n</i> (%)			
Adult	12 (60)	47 (26)	59 (29)
Child	8 (40)	128 (70)	136 (67)
Unknown	0 (0)	7 (4)	7 (3)
Suspected drug, <i>n</i> (%)			
Unknown penicillin	18 (90)	169 (93)	187 (93)
Ampicillin	0 (0)	1 (1)	1 (0)
Pivampicillin	0 (0)	2 (1)	2 (1)
Amoxicillin	1 (5)	4 (2)	5 (2)
Phenoxymethylpenicillin	1 (5)	6 (3)	7 (3)
Status of IgE at DPT, <i>n</i> (%)			
slgE not available	2 (10)	17 (9)	19 (9)
Interval from 1 dose to symptom onset, <i>n</i> (%)			
<1 day	4 (20)	19 (10)	23 (11)
1–3 days	3 (15)	28 (15)	31 (15)
>3 days	2 (10)	10 (5)	12 (6)
Unknown	11 (55)	125 (69)	136 (67)
Unknown symptoms, <i>n</i> (%)	1 (5)	36 (20)	37 (18)
Skin symptoms, <i>n</i> (%)			
Yes	19 (95)	144 (79)	163 (81)
Unknown	1 (5)	38 (21)	39 (19)
Type of rash, <i>n</i> (%)			
Flushing	0 (0)	4 (3)	4 (2)
Uncharacterized	4 (21)	64 (44)	68 (42)
MPE	15 (79)	76 (53)	91 (56)
Duration of MPE, <i>n</i> (%)			
<3 days	3 (20)	17 (23)	20 (22)
3–7 days	6 (40)	16 (21)	22 (24)
Unknown	6 (40)	42 (56)	48 (53)
Treatment, <i>n</i> (%)			
No	9 (45)	80 (44)	89 (44)
Yes	4 (20)	18 (10)	22 (11)
Unknown	7 (35)	84 (46)	91 (45)

DPT, drug provocation test; MPE, maculopapular exanthema; slgE, specific IgE to penicillins.

Outcomes

Primary outcome: proportion of patients presenting a severe allergic reaction to the drug provocation. Severe allergic reactions were defined as anaphylaxis or severe cutaneous adverse reactions (SCARs).

Secondary Outcomes

- Proportion of patients with a confirmed non-severe allergic reaction to the drug provocation.
- Proportion of de-labeled patients.
- Proportion of patients without specific IgE values.
- Patients' certainty about having penicillin allergy before and after provocation.
- Patients' willingness to take penicillin again before and after provocation.

Retrospective Study Population

The risk stratification criteria used in the prospective study were applied to the department's drug allergy database, and low-risk patients were identified. The database consists of clinical information about >5,000 patients who have been evaluated for drug allergy at the department since 2013. Only patients ≥18 years of age at the time of DPT, with the same suspected culprit drugs as in the prospective part of the study, were included in the analysis. For further methodological description of the database, selection of this retrospective population, and analysis, see methods in online supplementary Material.

Statistical Methods

Statistical calculations were performed in the statistical program R. Statistical analyses were primarily descriptive. The χ^2 test was performed on the positive drug provocation rate in the low-versus high-risk group in the retrospective cohort. *p* values of less than 0.05 were considered statistically significant.

Results

Prospective Study Population

Index Reaction

In total, 202 patients were consecutively recruited to direct oral provocation. Most patients (*n* = 187, 93%) could not specify the culprit type of penicillin, see Table 2. All patients underwent a DPT with amoxicillin, regardless of the reported culprit drug. Some patients (*n* = 37, 18%) did not remember the symptoms at the index reaction, but most patients (*n* = 163, 81%) reported skin symptoms, most often uncharacterized (*n* = 68, 42%) or MPE (*n* = 91, 56%). Seven patients (3%) had tolerated another type of penicillin, and one of these patients had a reaction on the DPT.

Specific IgE to Penicillin

The majority of patients (*n* = 183/202, 91%) had been tested for sIgE by their GP before referral, and all 183 patients had values below 0.35 kUA/L.

Drug Provocation Tests

Out of the 202 patients, 20 (10%, CI: 7%–15%) had a positive DPT, but none (0/202, 0%, CI: 0%–2%) had anaphylaxis or a severe delayed hypersensitivity reaction. Out of the reactions, four (20%, CI: 8%–42%) were mild IR, see Table 3. One patient (patient X) developed symptoms 1 h after intake, which were attributed to hyperventilation with tingling of lips and fingers, feeling of tightening in the throat, flushing, and dizziness. Symptoms resolved without treatment, and there were no skin symptoms or changes in blood pressure or peak flow. The patient declined re-provocation and could thus not be de-labeled and is included as allergic in this study despite the very low probability of allergy.

The three other IR developed 1–2 hours after the first dose. One patient developed urticaria and responded well to oral antihistamines and steroids. The second patient developed localized pruritus and flushing on the neck and left arm and responded well to antihistamines. The third patient (patient Y), who had not been tested for sIgE before DPT, developed flushing, heat sensation, and tingling of the lips at DPT, and even though symptoms were

Table 3. Details about reactions during provocation for allergic patients in the prospective study population (*n* = 20)

	Allergic (<i>n</i> = 20)
Female, <i>n</i> (%)	16 (80)
Age, median (IQR), years	45 (31–60)
Type of reaction during provocation, <i>n</i> (%)	
Immediate reaction	4 (20)
Delayed reaction	16 (80)
Interval from first dose to symptom onset, <i>n</i> (%)	
<1 day	5 (25)
1–3 days	2 (10)
>3 days	13 (65)
Skin symptoms, <i>n</i> (%)	
Yes	19 (95)
No	1 (5)
Type of rash, <i>n</i> (%)	
Flushing	2 (11)
Uncharacterized	2 (11)
Urticaria	2 (11)
MPE	13 (68)
Duration of MPE, <i>n</i> (%)	
3–7 days	3 (23)
>7 days	8 (62)
Unknown	2 (15)
Treatment, <i>n</i> (%)	
Yes	18 (9)
No	2 (10)
Type of treatment, <i>n</i> (%)	
Only antihistamine	4 (22)
Antihistamine and oral steroids	9 (50)
Antihistamine and oral steroids and local steroid	4 (22)
Others, <i>n</i> (%)	1 (6)
DPT, drug provocation test; MPE, maculopapular exanthema.	

mild and difficult to conclude as allergic in hot surroundings, the patient was treated with oral antihistamines and steroids.

One patient developed a reaction within 24 h of the first dose with redness and pruritus on the palms and soles as well as swollen fingers. Symptoms responded to treatment with antihistamines. The remaining 15 reactions on DPT developed 1–3 days (*n* = 2) or >3 days (*n* = 13) after the first dose. One patient developed urticaria, and 13 patients developed MPE. All but 2 patients with MPE were treated with antihistamines and oral steroids. One patient (patient Z) reported an uncharacterized rash less likely to be allergic. The patient self-treated with local steroid, declined a re-provocation, and is included as allergic in this study despite low probability of allergy. If the 3 patients (X, Y, and Z) with

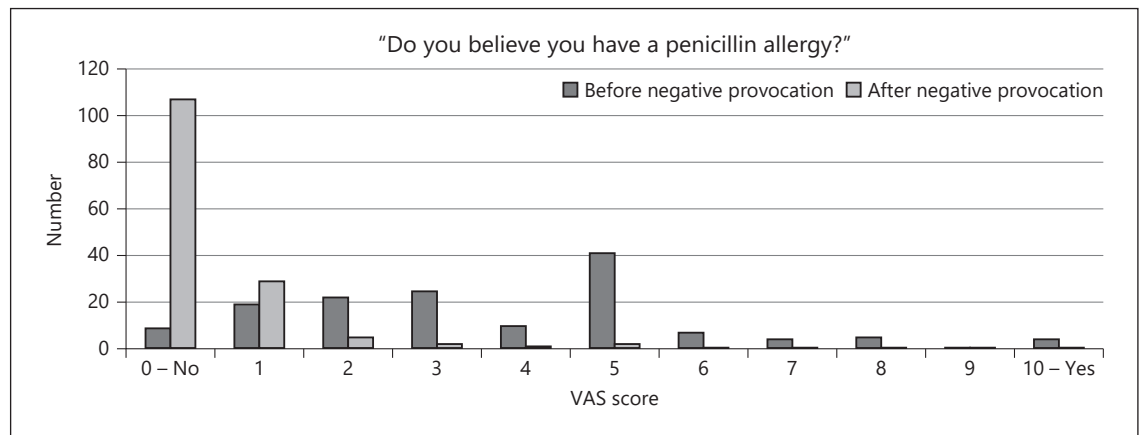


Fig. 1. Responses to question “How sure are you about having a penicillin allergy?” before and after a negative prolonged drug provocation test. Ten corresponds to “I believe I have penicillin allergy,” and 0 corresponds to “I do not believe I have penicillin allergy.”

symptoms less likely to be allergic were not considered allergic, there would be a total of 17 positive DPTs (8% CI: 5%–13%) in this study. Of the 19 patients, who had not been tested for sIgE before DPT, 2 patients (11%, CI: 3%–31%) developed a reaction during DPT, one with an IR (patient Y) and the other with an MPE lasting >3 days.

Patient Questionnaire

In total, 146 patients answered both pre- and post-provocation questionnaires, and 181 answered the pre-provocation questionnaire only. For the 146 full responses, the most frequent answer to the question about having a penicillin allergy was 5 before the DPT and 0 after DPT, as shown in Figure 1. In total, 19% ($n = 28/146$) answered that they would take penicillins outside of the allergy clinic before undergoing DPT, and all patients ($n = 146/146$) said that they would take penicillins after completion of an uneventful DPT. The most common reason ($n = 83/100$) for not wanting penicillin before DPT was due to “fear of an allergic reaction.” The most frequent answer to the question about feeling safe about future penicillin use, when prolonged DPT was negative, was 10 both before and after DPT (data not shown). All but 2 of the patients ($n = 144/146$) who answered the questionnaire stated that they had taken all the pills prescribed for prolonged provocation.

Retrospective Study Population

In the database, we identified 3,213 adult patients who had undergone a DPT with an aminopenicillin or penicil-

lin V/G. The same low-risk criteria that were used in the prospective study were applied and were fulfilled for 1,759/3,213 (55%). Out of the 1,759 patients, 183 (10%) patients had a reaction on DPT. There were no cases of anaphylaxis or severe delayed hypersensitivity reactions (0/1,759, CI: 0%–0%). There were 16 IR (9%, CI: 5%–14%), and all but 2 ($n = 14/16$) patients had skin symptoms as the only symptom. The 15th patient had skin symptoms, globus sensation, and dizziness, which was successfully treated with oral antihistamine and steroids. The 16th patient did not develop skin symptoms but had a decrease in peak flow and responded well to treatment with oral antihistamines and inhaled bronchodilator. For further details on the retrospective cohort, see online supplementary Table 1. The remaining patients in the retrospective population were considered high risk, and in this group, a higher proportion 252/1,454 (17%) were considered allergic after graded DPT ($p < 0.001$ between the low- and high-risk group).

Discussion

This paper describes the result of a safe, rapid, and relatively inexpensive risk stratification strategy for de-labeling a well-characterized group of patients with a low risk of penicillin allergy using direct untitrated oral provocation without skin testing. We also showed that low-risk patients were not worried about future treatment with penicillin following uneventful prolonged provocation and that compliance with prolonged provocation

was high. The overall rate of allergic reactions on direct oral provocation in the prospective study was 10%, and there were no severe allergic reactions – no anaphylaxis or SCARs. Three patients ($n = 3/202$, 1%) had symptoms after DPT with a low probability of being allergic and excluding these results in an overall rate of positive DPTs of 8%.

To assess the risk stratification criteria in a larger cohort, we applied the criteria to the drug provocation database in the department. Using the same inclusion criteria about age and culprit drugs as in the prospective cohort, we identified 3,213 patients, of which 1,759 (55%) matched the low-risk criteria used in the prospective study. Results from this large retrospective low-risk cohort were identical to results from the prospective study with respect to the rate of positive DPTs, the limited number of IR, and no cases of anaphylaxis or severe delayed hypersensitivity reactions. Although there is not yet consensus on the most optimal low-risk criteria, these results confirm the great potential of using risk stratification as a useful, safe, and effective de-labeling tool as more than half of the patients in the database fulfilled the low-risk criteria.

The proportion of confirmed allergies in our study is higher than in other low-risk studies [16, 45–50] and is most likely due to differences in patient selection and provocation procedure. Some studies include patients with a family history of penicillin allergy or nonallergic gastrointestinal side effects, headache, yeast infections, etc., who are unlikely to have a penicillin allergy, and including such patients will decrease the proportion of confirmed allergies [16, 49–51]. Only few studies have addressed this, suggesting that patients unlikely to have penicillin allergy do not need to undergo allergy testing before de-labeling [36, 45, 46]. Such an approach will potentially save valuable time and resources for allergy investigation, and this group of patients should be investigated further in larger studies to determine safe criteria for direct de-labeling by GPs or other doctors managing such patients. Another reason for the relatively high positivity rate in our study is likely to be the routine use of prolonged provocation [16, 45–48, 52]. The benefits, such as better compliance with subsequent treatments, and disadvantages, such as increased risk of antibiotic resistance, of prolonged provocation are still discussed in the literature, and there is not yet consensus on the optimal DPT protocol [4, 28, 43, 53–58]. A higher risk of de-novo sensitization during prolonged provocation might be hypothesized. Follow-up studies should investigate whether de-labeling with a single dose underestimates nonim-

mediate allergy and whether patients de-labeled with a single-dose provocation are more likely to develop nonimmediate reactions during subsequent treatment with penicillins.

Patients in both the de-labeled group and the allergic group had a long interval between the index reaction and allergy testing. This means that our findings may not be directly extrapolated to a cohort of patients with more recent reactions.

As the risk stratification criteria excluded patients considered at risk of an IR, a nontitrated DPT was chosen. As expected, it proved to be safe, whilst minimizing waiting time for patients and optimizing staff resources.

In the majority of cases (93%), patients did not recall the suspected culprit type of penicillin. We chose to challenge with amoxicillin, as this would identify allergy to the beta-lactam ring as well as to the side chains, which are the more common allergenic epitopes. In theory, this strategy might have resulted in patients specifically allergic to penicillin V or G not being identified. Such patients are expected to be rare.

There is presently no consensus on the criteria for stratifying patients to the low-risk category [28, 32, 59]. All agree on the exclusion of severe cutaneous reactions and systemic involvement, but more detailed clinical pictures differ [34, 60–64].

It is often difficult to characterize skin eruptions and distinguish urticaria elicited by an IgE-mediated allergy from a benign rash. Some groups therefore recommend that all patients with nonsevere cutaneous eruptions should be considered moderate risk [61]. A recent study investigated 410 patients (adults and children) with urticaria during treatment with a beta-lactam antibiotic, and they showed that timing and duration of urticaria is relevant and that patients with onset of urticaria within 1 h of the first dose and with shorter duration than 1 day are significantly more likely to test positive on provocation and should be considered high risk [65]. In another study, 134/143 adult patients with a “benign” rash (including urticaria) more than 1 h after the first dose tolerated penicillin challenges (2-day challenge for delayed reactions). The authors state that only 9% presented initially with urticaria, and the majority of these had a diagnosis of chronic spontaneous urticaria [51]. In our study of adult patients, urticaria was considered high risk regardless of timing of onset, but as delayed-onset urticaria is relatively rare in adults compared to children, we only excluded few patients due to urticaria.

Some patients ($n = 36$, 18%) did not recall any details about the index reaction. In this patient group, only 1 pa-

tient (3%) was confirmed allergic to penicillin by developing a longer lasting MPE at DPT. It is important that patients with a vague or unknown history of allergic reactions undergo drug allergy investigation, and they may safely be included in the low-risk category. If index reactions had included severe symptoms, it is very likely that the patients would have remembered.

It is important to recognize that no reactions were characterized as severe reactions in our two cohorts totaling 1,961 de-labeled patients, and benign MPEs were the most common presentation after DPT. Some countries report aminopenicillins to be a common cause of anaphylaxis [66, 67], while other countries mainly see benign reactions, like MPEs [4, 61, 64]. Geographical differences in exposure or genetics may play a role in the allergic reaction patterns to amoxicillin. This requires further studies and must be taken into consideration when implementing risk stratification as a tool in allergy departments in different countries.

Since there were no cases of anaphylaxis, neither in the prospective nor the retrospective low-risk cohort, health professionals might consider treating low-risk penicillin allergy patients with penicillin without preceding tests, when indicated during hospital submission, under appropriate observation. The benefits of penicillin treatment would outweigh the consequences of an, in worst case, MPE. However, it is important that patients feel safe, and that follow-up is available, in case of onset of a delayed allergic reaction when the patient has left the hospital.

Other studies have examined the possibility of different professionals, such as pharmacists, performing de-labeling [6, 68, 69]. Although no severe allergic reactions occurred in this study, there was at least one case of hyperventilation with subjective symptoms such as tingling of lips and fingers and feeling of tightening in the throat which could have been misinterpreted as anaphylaxis. Differentiating hyperventilation/anxiety or vasovagal reactions from a true anaphylactic reaction requires health care personnel with experience in allergic reactions, regardless of the professional group. So, although the risk of an immediate allergic reaction is low, penicillin allergy de-labeling among low-risk patients should still be performed in a setting with access to allergy advice to ensure correct interpretation of symptoms.

We performed prolonged oral provocation without preceding skin testing, thereby avoiding the risk of potentially false-positive skin tests discussed by other groups [45, 70]. In Denmark, previous guidelines recommended specific IgE analyses in all patients, and the majority of patients had confirmed negative sIgE to penicillins ahead of referral. Pa-

tients with elevated sIgE for one or more penicillins might not have been referred, and this potentially introduces selection bias. However, IgE-positive patients would be expected to have IR and most likely urticaria, respiratory, and circulatory symptoms, and all of these were exclusion criteria in this study [71, 72]. One patient who was excluded from the study due to positive sIgE for amoxicillin (0.39 kUA/L) was later de-labeled with a DPT, outside of this study, with amoxicillin including prolonged provocation with amoxicillin 500 mg $\times$ 2 for 2 days.

Previous studies have shown that even though patients are safely de-labeled during allergy investigation, some are hesitant to receive future treatment with penicillin [41–44]. This was addressed in this study, and almost none of the de-labeled patients were worried about future penicillin treatment, which is also seen in a recent study [73]. Responses from the questionnaires confirmed that the majority (98%) of patients reported to have completed the prolonged challenge, which is higher than in a previous study, where 9% stopped treatment before completion [70]. Questionnaires were performed face-to-face before DPT and by phone or email after completion of prolonged provocation. Bias to “please the interviewer” may influence the results, but we believe that reluctance toward future penicillin treatment after de-labeling is rare in a group of low-risk patients evaluated with a prolonged provocation. Future studies must determine whether reluctance toward penicillin treatment is more frequent among high-risk patients or after single-dose provocation [74].

Conclusion

Our risk stratification criteria for identifying low-risk patients for oral drug provocation test without prior skin testing are safe, and there were no cases of anaphylaxis or SCARs in a large combined prospective and retrospective cohort. Delayed reactions still occur in our Danish cohort, and these are important to recognize and treat. Penicillin de-labeling among low-risk patients should therefore be performed in a setting with access to allergy advice to ensure correct diagnosis and adequate follow-up. After de-labeling with prolonged provocation, low-risk patients reported not to fear future penicillin intake.

Statement of Ethics

The prospective study protocol was reviewed and approved by the Hospital Administration at Herlev and Gentofte Hospital, Hellerup, Denmark (Workzone No. 9075674), and written informed

consent was obtained from patients. The retrospective study was performed under the existing database and project approval from the Regional Centre for Research Approvals (Jr.nr. P-2019-390), which includes exemption from written informed consent from patients. Under the Danish law, ethical approval was not required for neither the prospective nor the retrospective study.

Conflict of Interest Statement

The authors declare that they have no relevant conflicts of interest.

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Author Contributions

L.H.G., H.F.M., and S.F. took initiative to the article with regard to the conception and design. S.F. and S.R. acquired data. S.F. and J.B.B. analyzed the data. S.F. drafted the first draft. L.H.G., H.F.M., J.B.B., and L.K.P. 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.

Data Availability Statement

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to restrictions, e.g., data containing information that could compromise the privacy of research participants.

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Table S1. Demographics and data about index reaction for low-risk patients from database (retrospective study population n=1759).

	Allergic (n=183)	Delabelled (n=1576)	Total (n=1759)
Female	151 (83%)	1090 (69%)	1241 (71%)
Age at DPT (median, IQR)	52 (37- 66)	49 (36- 62)	49 (36- 62)
Years between index reaction and DPT (median, IQR)	16 (2-31)	25 (6-39)	25 (5-39)
Adult/child at index reaction			
Adult	123 (67%)	749 (48%)	872 (50%)
Child	43 (23%)	703 (45%)	746 (42%)
Unknown	17 (9%)	124 (8%)	141 (8%)
Suspected drug at index reaction			
Unknown penicillin	13 (7%)	43 (3%)	56 (3%)
Ampicillin	6 (3%)	14 (1%)	20 (1%)
Pivampicillin	36 (20%)	70 (4%)	106 (6%)
Amoxicillin	53 (29%)	199 (13%)	252 (14%)
Phenoxyethylpenicillin	59 (32%)	1174 (74%)	1233 (70%)
Benzylpenicillin	1 (1%)	9 (1%)	10 (1%)
Amoxicillin/clavulanic acid	15 (8%)	67 (4%)	82 (5%)
Drug used for DPT			
Ampicillin	6 (3%)	15 (1%)	21 (1%)
Pivampicillin	36 (20%)	71 (5%)	107 (6%)
Amoxicillin	66 (36%)	241 (15%)	307 (17%)
Benzylpenicillin	0 (0%)	9 (1%)	9 (1%)
Phenoxyethylpenicillin	60 (33%)	1178 (75%)	1238 (70%)
Amoxicillin/clavulanic acid	15 (8%)	62 (4%)	77 (4%)
Status of sIgE at DPT			
Negative sIgE	181 (99%)	1566 (99%)	1747 (99%)
One or more positive sIgE	2 (1%)	10 (1%)	12 (1%)
Interval from 1. dose to symptom onset (index)			
<1 day	13 (7%)	114 (7%)	127 (7%)
1-3 days	39 (21%)	275 (17%)	314 (18%)
>3 days	78 (43%)	409 (26%)	487 (28%)
Unknown	53 (29%)	778 (49%)	831 (47%)
Unknown symptoms	5 (3%)	171 (11%)	176 (10%)
Skin symptoms (index)			
No	6 (3.3%)	46 (2.9%)	52 (3.0%)
Yes	169 (92.3%)	1327 (84.2%)	1496 (85.0%)
Unknown	8 (4.4%)	203 (12.8%)	211 (11.9%)
Type of rash (index)			
No rash	2 (1%)	42 (3%)	44 (3%)
Flushing	13 (8%)	61 (5%)	74 (5%)
Uncharacterized	67 (40%)	628 (47%)	695 (46%)
Other	5 (3%)	60 (5%)	65 (4%)
MPE	82 (49%)	536 (40%)	618 (41%)
Duration of MPE (index)			
<3 day	5 (6%)	9 (2%)	14 (2%)
3-7 days	6 (7%)	15 (3%)	21 (3%)

>7 days	2 (2%)	2 (0%)	4 (1%)
Missing data	67 (84%)	510 (95%)	579 (94%)
Treatment (index)			
No	72 (40%)	661 (42%)	733 (42%)
Yes	54 (30%)	237 (15%)	291 (17%)
Unknown	57 (30%)	678 (43%)	735 (42%)

DPT=drug provocation test, Index= Index reaction, MPE=maculopapular exanthema sIgE=specific

IgE to penicillins