



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Original Article

Drug-specific history, skin and *in vitro* tests can reduce the need for drug provocation tests in betalactam-hypersensitivity

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ARTICLE INFO

Article history:

Received 16 August 2020

Received in revised form

17 September 2020

Accepted 24 September 2020

Available online xxx

Keywords:

Adverse drug reaction

Cephalosporin

Penicillin

Skin test

Specific IgE

Abbreviations:

ADR, adverse drug reaction; DHR, drug hypersensitivity reaction; DPT, drug provocation test; dsIgE, drug specific IgE; PT, patch test; sIgE, specific IgE; SPT, skin prick test

ABSTRACT

Background: Many patients report questionable drug hypersensitivity reactions (DHR) to betalactam antibiotics. A workup is required for objectivation. Direct drug provocation tests (DPTs) omitting a prior allergy workup are increasingly recommended as the primary diagnostic approach. However, apart from the risk of severe side effects, DPTs often are a scarce resource in overloaded healthcare-systems. We investigated how many cases can be solved by drug-specific history, drug-specific IgE, and skin tests obviating the need for DPT.

Methods: We conducted a chart review in a retrospective cohort of 932 patients in an allergy outpatient centre from 2016 to 2017. Patients had been submitted to drug-specific history and specific IgE-, skin prick-, intradermal- and patch-tests with early and late readings with a series of penicillins and cephalosporins but DPTs were no option.

Results: Overall, positive *in vitro* and/or skin tests were found in 96/932 (10.3%) patients. Drug-specific IgE was detected in 40/932 (4.3%) patients, 61/787 (7.8%) patients had positive skin tests. *In vitro* tests to Penicillin V showed the highest rate of positivity 24/479 (5.0%) and early readings of ampicillin the highest amongst the skin tests (3/49, 6.1%). Immediate skin tests were more often positive than delayed ones (75:45). The combination of all parameters including drug-specific history solved 346/932 (37.1%) cases while 586/932 (62.9%) remained unresolved. Self-reported DHR could be less often confirmed in females and young children ($p < 0.05$).

Conclusions: Testing with betalactams applying simple, cheap, and safe skin and blood tests can solve a third of DHR-cases on a high throughput scale.

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Introduction

About 10% of the population reports a drug hypersensitivity reaction (DHR) to β -lactam antibiotics including penicillins and cephalosporins (Structure [Supplementary Fig. 1](#)).¹ However, only 4% of these patients will show positive reactions when tested with penicillin either by skin, blood or provocation tests.² Several reasons explain this high rate of false histories:

1. Most adverse reactions are caused by the specific pharmacological mechanism of the antibiotic and are classified as non-allergic type A reactions, e.g. gastrointestinal malfunction. Type A reactions comprise more than 80% of all DHR and are no

contraindication for a future reintroduction of the suspected drug even without testing.^{3,4}

2. True allergic reactions (B-type³) are usually regarded as contraindications for future use. They may be of the immediate, anaphylactic type I (IgE-mediated), or of the delayed type IV (T-cell mediated). However, immunological memory may wane and completely disappear over the years.⁵
3. Differential diagnoses such as urticaria/angioedema driven by infection⁶ and viral exanthema are much more frequent than DHRs.⁷ Infection may lead to the prescription of antibiotics and a skin reaction might be misinterpreted as being caused by the drug especially by non-dermatologists and non-allergologists.

Unevaluated DHRs bear considerable risks not only for the patient, who may unnecessarily receive alternative, less effective antibiotics, but also for the society because the overuse of alternative antibiotics can propagate antibiotic resistance.^{8,9} Hence, current guidelines on the management on DHRs demand a workup

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Peer review under responsibility of Japanese Society of Allergology.

<https://doi.org/10.1016/j.alit.2020.09.010>

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for “de-labelling” of false histories of DHR for relevant drugs and β -lactam antibiotics are generally regarded as being such of a kind.^{3,10}

There seems to be some disagreement on how to reach this goal on both sides of the Atlantic.¹¹ While European and US-experts agree on the importance of skin testing, there are different views on the usefulness of *in vitro* tests.¹² Skin tests offer the advantage of giving an immediate result and are cheap for the healthcare system.¹³ While their sensitivity is limited, their specificity is high.¹⁴ *In vitro* tests give the advantage of being safest. Unfortunately, there is only a limited number of standardized tests available. Measurement of specific IgE (sIgE) has a low sensitivity but a high specificity.¹⁵

DPTs are the gold standard of drug hypersensitivity reactions as outlined in many national and international guidelines.^{3,16,17} Nevertheless, they are no perfect tests concerning resources, safety, and costs. During a DPT, a patient will receive a drug in an “off-label” setting. Hence, a maximum of safety requirements has to be provided which is usually in a hospital setting with backup resuscitation facilities.^{17,18} Hence, DPT are scarce resources in most healthcare systems leaving many patients without evaluation for many years.

DPTs also produce higher costs. In 2018, a basic DHR test without drug provocation tests (DPT) was calculated causing costs of US\$ 220 for the US healthcare system. Including DPTs increased the price to at least US\$ 359.¹⁹ Nevertheless, some North American experts have recently started propagating DPTs for mild reactions even without prior skin or *in vitro* tests.^{9,20–23} However, because of the bottleneck of limited amount of specialised provocation centers, this approach may even make the situation worse because of increasing waiting times for undiagnosed patients.

With this study we wanted to take a step back. Hence, we were interested, how many cases of suspected DHRs to β -lactams could be solved by applying simple, widely available tools such as skin tests and measurement of specific IgE before performing DPTs in order to reduce the pressure on the provocation centers. We report the results of a retrospective chart review of a cohort of 932 patients with a history of DHRs to β -lactam from the years 2016–2017 from a single centre outpatient clinic.

Methods

Patients

From January 1st, 2016 to December 31st, 2017 a cohort of 48.629 routine patients or sera of routine patients were referred to

the Floridsdorf Allergy Center counting 91.438 diagnoses. Of these, 3.875 (8.0%) carried a diagnosis compatible with a DHR-history. In 1.532 individuals the suspected drug belonged to penicillin and/or cephalosporine antibiotics and a serological test was made. Because the laboratory of the allergy clinic also serves as a tertiary referral centre for external, serological tests, clinical data was not available for 76 patients who were eliminated leaving 1456 subjects for the intention-to-treat analysis (Fig. 1). A further significant number of 523 persons had to be excluded from the per-protocol analysis because they did not show up for scheduled skin tests and another single patient stepped down from skin testing later (low compliance). This resulted in 932 individuals available for the per-protocol analysis (Table 1, Fig. 1).

Figure 2 depicts the workup-algorithm, modified according to the guideline of the German speaking countries.²⁴ The attending physicians could deviate from this algorithm according to patient-specific needs. They also determined primary outcome (DHR ‘confirmed’, ‘possible’, or ‘unresolved’) integrating and interpreting the summary of all test results.

Materials and methods

Total IgE, sIgE and serum tryptase were measured on an ImmunoCAP 250 laboratory system with commercially available tests bought from ThermoFisher (Uppsala, Sweden): Penicilloyl G (c1) & V (c2), Amoxicilloyl (c6), Ampicillin (c5), Minor determinate mixture (MDM) (U233), Cefaclor (c7). Due to manufacturer’s production shortages not all test reagents were available during the whole study period (especially MDM, Ampicillin and Cefaclor).

Skin prick (SPT), intradermal (IDT) and patch tests (PT) were performed with nationally licensed drugs for intravenous use in nationally recommended concentrations and read accordingly^{16,24,25}: Penicillin G, Amoxicillin/Clavulanic Acid, Cefazolin and Ceftriaxone: “Penicillin G-Natrium Sandoz”, “Curam®”, “Cefazolin

Table 1

Study patients as defined by the per-protocol analysis in Figure 1. Age was defined as the age at the 1st presentation in the allergy clinic.

Age [a]	Female [n]	Male [n]	F:M Ratio	Σ [n]
0–10	57	58	0.98	115
11–20	47	26	1.81	73
21–40	168	50	3.36	218
41–60	228	73	3.12	301
>60	169	56	3.02	225
Σ [n]	669	263	2.54	932

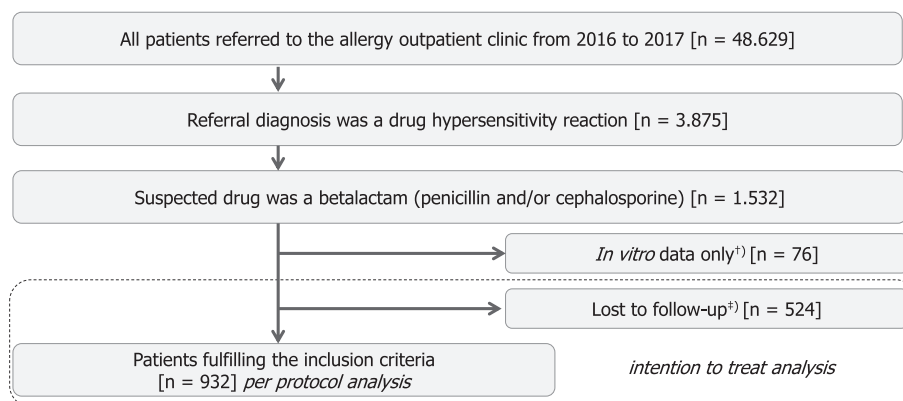


Fig. 1. Definition of patient-populations. Flow diagram and definition of the patient populations. † 76 blood samples had been sent in by external physicians to the reference allergy laboratory without clinical data, why these data sets were excluded from the analysis. ‡ 523 patients who did not show up for their scheduled skin tests +1 patient refusing skin tests.

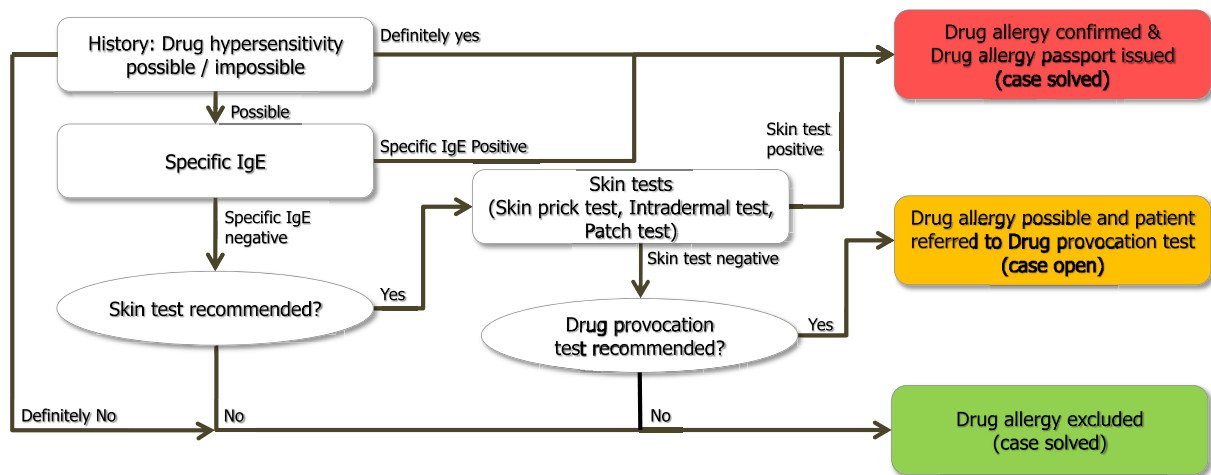


Fig. 2. Flow chart. Algorithm for the workup of the study patients. Each individual physician could deviate from this procedure according to the patient's individual needs. Drug provocation tests were not part of this study.

Sandoz", "Ceftriaxon Sandoz", all from Sandoz, Kundl, Austria; Ampicillin/Sulbactam: "Unasyn®", Pfizer, Borgo San Michele, Italy; Cefuroxim: "Cefuroxim MIP", Cephasaar, Sankt Ingbert, Germany). SPT, IDT (0.03 ml) and PT were performed using the following concentrations diluted in sterile *Aqua destillata*: Penicillin G [10.000 IU/ml], Amoxicillin/Clavulanic Acid & Ampicillin/Sulbactam [20 mg/ml]; Cefazolin/Cefuroxim/Ceftriaxon [2 mg/ml].

The commonly used penicillin derivatives MDM & PPL for skin tests marketed by Diater, Madrid, Spain are not licensed in Austria and cannot be used in routine settings outside academic hospitals. PTs were performed using Curatest® (Lohman und Rauscher, Vienna, Austria) and read after 24 h together with the late reading of the IDT.

Skin tests were done in the following order: 1st) all SPTs at once, when negative after 20 min followed by, 2nd) all IDTs at once, when negative after 20 min followed by, 3rd) all PTs at once followed by, 4th) late readings of all tests after 24 h.

Ethics and statistics

The study was approved by the ethics committee of the Medical University of Vienna, Austria, during Christian Ostermayer's medical diploma thesis according to the Helsinki Declaration of Human Rights (ECS 1103/2018). χ^2 -Tests were calculated using MedCalc Statistical Software version 19.2 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2020).

Results

Patients

There were 932 cases (669 female/263 male; 42.5 years old $\pm$ 22.1) for the per protocol analysis. In 796/932 cases (85.4%) the suspected index drug was a penicillin, in 136 (14.6%) a cephalosporin. While the sex ratio was balanced in children of up to 10 years, the rate of female patients steadily increased from teenagers to peak at a ratio of 3 females per 1 male in adults (Table 1).

A DHR could already be excluded by history in 135/932 patients (14.5%) before entering the allergy workup. In most cases, the patients had unintentionally but safely reintroduced a β -lactam e.g. in the form of a generic drug under a different brand name.

Two patients had reported a history of a severe cutaneous adverse reaction (SJS/TEN) of whom one was patch

tested negatively. Many patients had a history of either an immediate DHR (<1h after drug intake, 243/932 (26.1%)) or a delayed DHR (>24h after drug intake) 365/932 (39.2%), the resting histories could not be allocated univocally (324/932 = 34.8%).

Specific IgE

Availability of dsIgE (drug specific IgE) was an inclusion criterion and 40/932 (4.3%) patients had at least one positive test above the standard cut off ≥ 0.35 kU/l (Table 2). In detail, there were 83/2227 (3.7%) positive sIgE tests. Surprisingly, Penicillin V and not Amoxicillin was the most often positively tested β -lactam (24/479 = 5.0%; Table 2, Fig. 3a). This well reflects the national preference for narrow spectrum antibiotic therapy with penicillin over broad spectrum antibiotics with aminopenicillins in order to reduce the propagation of antibiotic resistance.²⁶ Measuring sIgE to minor determinants mixture MDM or Cefaclor added little value in the diagnosis of type I allergy to β -lactams.

It is known that sensitivity and specificity of dsIgE to β -lactams is influenced by total IgE.^{27,28} The calculation of a dsIgE/total IgE-ratio had been suggested to overcome unspecificity in high total IgE. Vultaggio *et al.* published a threshold of >0.0022 with a sensitivity of 43%, a specificity of 95%, and a positive predictive value of 93% for the β -lactam ImmunoCAP® assays.²⁹ We found elevated total IgE of ≥ 100 kU/l in 244/917 (26.6%) sera. Applying the hypothetical 0.0022 dsIgE/total IgE-ratio would have increased the positivity rates to Amoxicilloyl (from 2.8% to 16.3%), Penicilloyl V (from 5.0% to 11.7%), Ampicillin (from 4.0% to 7.5%) and Cefaclor (1.0%–6.3%) but not to Penicilloyl G and MDM (grey columns in Fig. 4).

Another recommendation is lowering the cut off from ≥ 0.35 kU/l to ≥ 0.1 kU/l¹⁵ to expand the sensitivity of sIgE especially in patients with low total IgE levels. This lower threshold level would have doubled the overall positivity rates from 83/2227 (3.7%) to 171/2227 (7.8%), doubled all penicillins and septupled cefaclor but left MDM sensitivity unchanged (Table 2, purple columns in Fig. 4). For the further per-protocol-analysis we decided to exclude both possibilities to maintain comparability with previous studies.

Interestingly, 7/365 (1.9%) of the patients with a history suggestive for a delayed type-response had drug-specific IgE suggesting rather an immediate than a delayed mechanism. Considering,

Table 2

. Overview of all test results in absolute and relative numbers: sIgE = specific IgE (positive/negative).

	sIgE [≥ 0.35 kU/l] /all [†]	Skin Prick Test 20min/all [‡]	Skin Prick Test 24 h/all [‡]	Intradermal Test 20min/all [†]	Intradermal Test 24 h/all [†]	Patch Test 24 h/all [†]
Penicillin G	16/376 4.3%	8/747 1.1%	1/747 0.1%	22/742 3.0%	3/742 0.4%	1/722 1.4%
Penicillin V	<u>24/479 5.0%</u>					
Amoxicillin	21/762 2.8%	11/742 1.5%	<u>7/742 0.9%</u>	22/737 3.0%	17/737 2.3%	11/716 1.5%
Ampicillin	16/402 4.0%	1/52 1.9%	<u>0/52 0%</u>	<u>3/49 6.1%</u>	<u>2/49 4.1%</u>	<u>2/51 3.9%</u>
MDM	5/111 4.5%					
Cefaclor	1/97 1.0%					
Cefazolin		<u>2/60 3.3%</u>	0/60 0%	2/57 3.5%	0/57 0%	1/50 2.0%
Cefuroxim		1/67 1.5%	0/60 0%	2/65 3.1%	0/65 0%	0/55 0%
Ceftriaxon		1/50 2.0%	0/60 0%	0/47 0%	0/47 0%	0/41 0%
Σ	83/2227 3.7%	24/1718 1.4%	8/1718 0.5%	51/1697 3.0%	22/1697 1.3%	15/1635 0.9%

Results of specific IgE (≥ 0.35 kU/l) is displayed in the first column. Prick and intradermal tests: 20 min/24 h/all tests. Patch tests 24 h/all. The highest value of each category is in underline format.

[†] IgE-mediated, immediate type I allergy.

[‡] T-cell mediated, delayed-type IV allergy.

that there were only 40 patients with a positive sIgE test, the history concerning the timing and type of DHR was not reliable in 17.5% (7/40), which can have consequences when assigning safety precautions during DPTs.

Skin tests

Skin tests were positive in 61/787 (7.8%) patients. IDTs were the most sensitive tests for both immediate ($\dagger$) and delayed reactions ($\ddagger$) (Table 2, Fig. 3c). Contrary to the *in vitro* tests, Aminopenicillins were more often positive than Penicillin G in early and late readings. This was true for SPT and IDT (Fig. 3b, c). Cephalosporines showed the relatively highest rate of positive SPTs (Fig. 3b). In our algorithm, a positive SPT in the immediate reading abrogated a continuation with IDTs (see Methods). That is why cephalosporins had lower rates of positive IDTs than aminopenicillins (Fig. 3c).

Overall, Ampicillin had the highest percentage of positive IDT reactions (Fig. 3c). This reflects the recent trend to turn away from prescribing Amoxicillin/Clavulanic acid back to the stronger allergen Ampicillin/Sulbactam due to its' high liver-toxicity.³⁰ Overall, Ampicillin had the highest percentage of positive IDT reactions (Fig. 3c).

PT showed low additive value to late readings of IDTs. There were only two cases, each with a history of maculopapular rash, where the PT rendered positive with an at the same time negative late reading of the IDT.

Safety

Safety is always a matter of concern when doing skin tests in patients with a history of DHR. In 5050 skin tests (1718 SPT, 1697 IDT, 1635 PT), we did not observe a single systemic reaction in any patient independent of the initial reaction pattern.

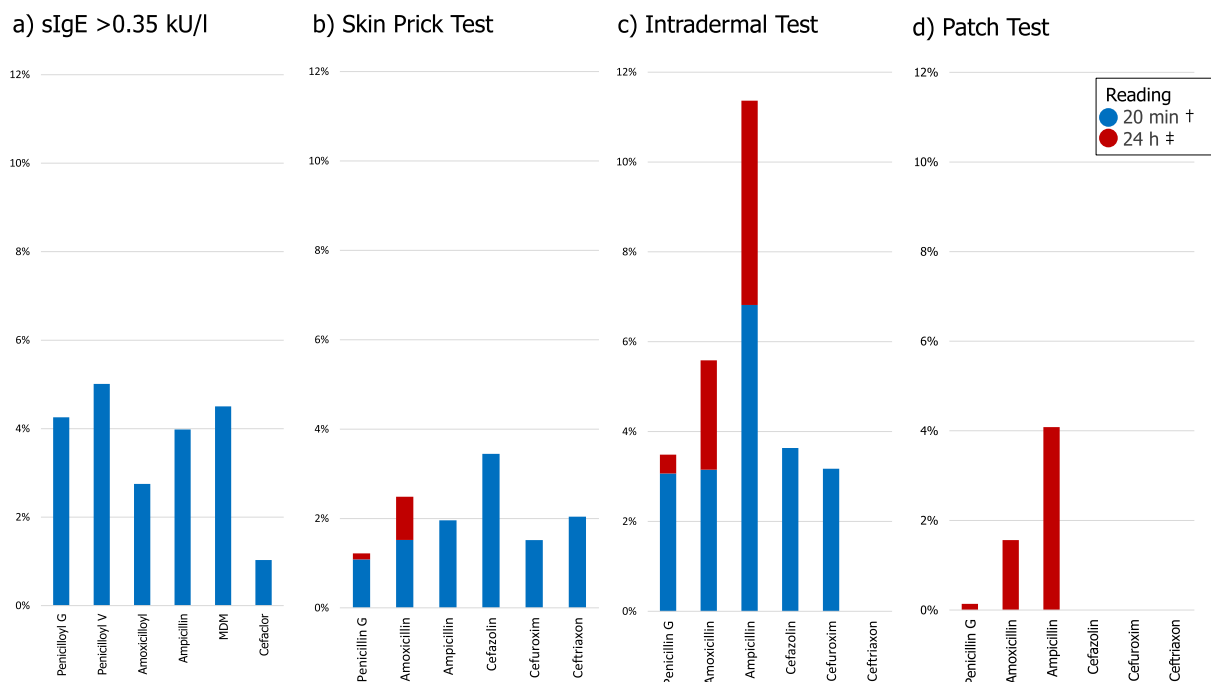


Fig. 3. Percentage of positive tests in relation to all tests. Positive tests for specific IgE (a) and early readings in skin prick tests (b) and intradermal tests (c) were suggestive for immediate type I allergy (● blue). Late readings (● red) in skin prick tests (b), intradermal tests (c) and patch tests (d) after 24 h were suggestive for delayed type IV reactions.

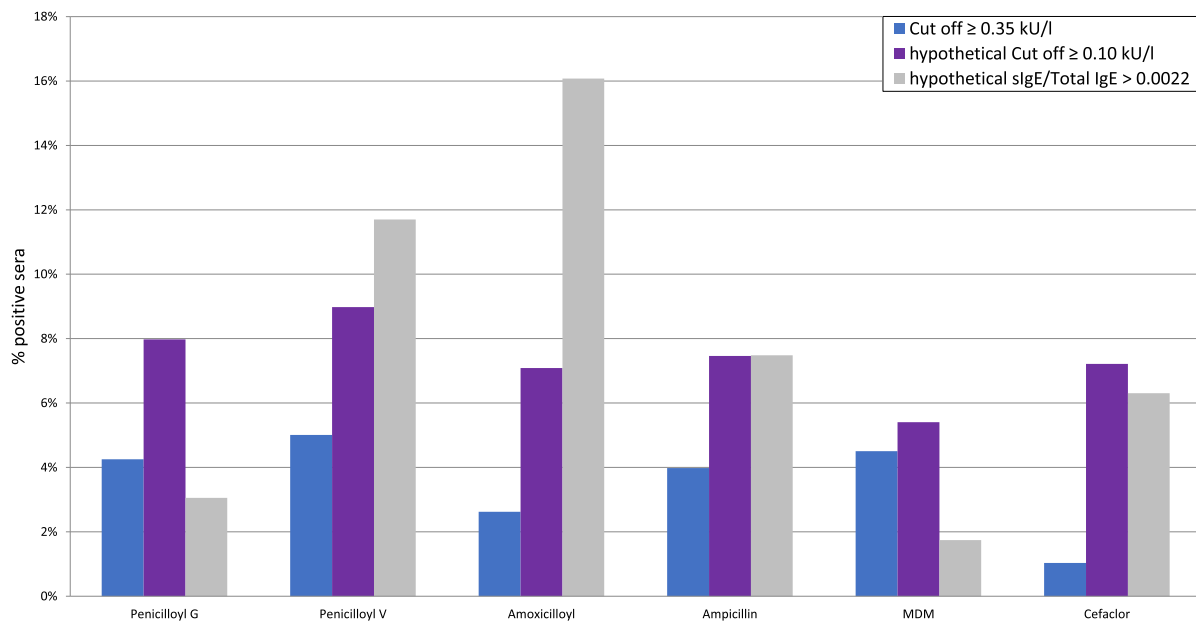


Fig. 4. Specific IgE to Beta-lactams. The hypothetical lowering of the standard threshold for drug-specific IgE from ≥ 0.35 kU/l (● blue) to ≥ 0.1 kU/l (● purple) is recommended by some guidelines to increase the weak sensitivity in patients with low total IgE.¹⁵ Another hypothetical indirect measure in patients with a high total IgE is to determine the sIgE/total IgE ratio. Vultaggio *et al.* published a cut off of >0.0022 for β -lactam antibiotics (● grey).²⁹

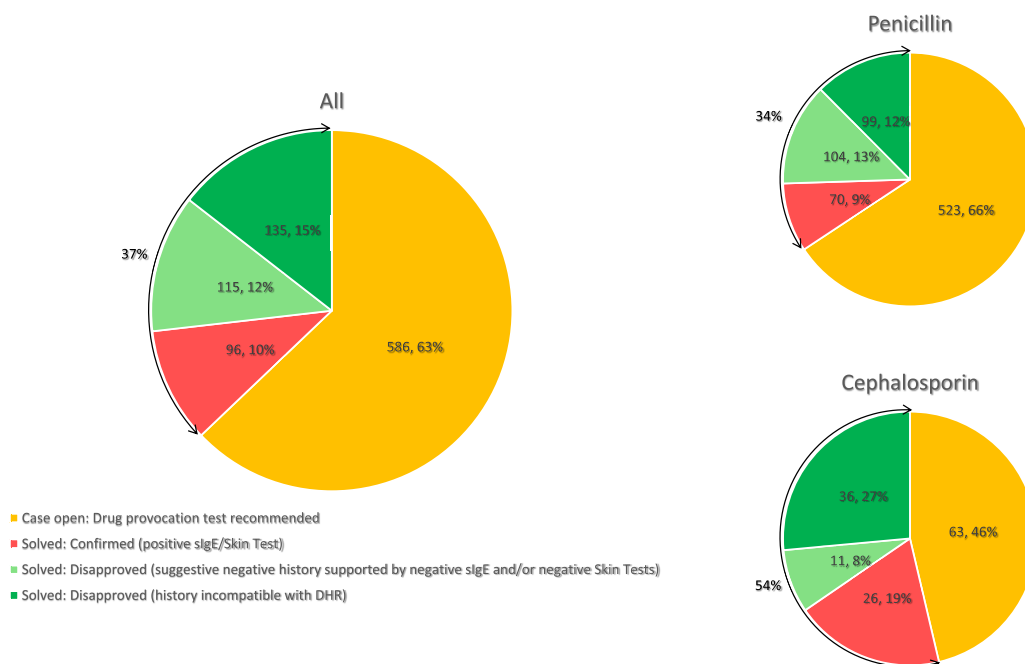


Fig. 5. How many cases were solved? As the primary endpoint of this study, it was possible to solve 37.1% of the cases (confirmed in ● green and disapproved in ● red) by exploiting all possibilities of the algorithm depicted in Figure 1. Penicillin and Cephalosporin differed as only 34% of the Penicillin but nearly half of the Cephalosporin cases could be solved.

Cross-reactivity of type I responses

Cross-reactivity within β -lactam antibiotics is caused by structural similarities (Supplementary Fig. 1). That is why many patients had more than one positive test. The 83 positive *in vitro* tests represented only 40 patients and the 120 positive skin tests only 61 patients. Only 2 patients had cross-reactions between penicillins and cephalosporins.

The amount of solved cases

This study asked for how many cases of DHR to β -lactams can be solved before performing a consecutive DPT: Of the 932 patients in the per-protocol-analysis, 135 (14.5%) had not been submitted to tests because the DHR could already be excluded by history (e.g. because a penicillin had already been unintentionally but safely

taken by the patients after the index reaction, Fig. 5). In another 115 patients (12.3%), a DHR could be ruled out by a very improbable history (e.g. implausible history for a DHR) further underlined by negative *in vitro* and *in vivo* tests. In 96 (10.3%) patients, drug allergy was confirmed by positive *in vitro* and/or *in vivo* test and the patients received an allergy passport, the usual way of handling this situation in central European countries.³¹ Summing up, 346 (37.1%) cases were successfully solved while 586 (62.9%) remained unresolved. Histories of DHR to cephalosporin were more often solved than the ones to penicillin (54% vs 34% Fig. 5).

A successful diagnostic procedure depended a lot on the patients' compliance. Although we tried to make the workup as convenient as possible, a case of DHR could usually not be resolved at the first visit. The intention-to-treat population also included the patients not showing up for their scheduled skin tests (Fig. 1). Including these patients markedly increased the numbers of unsolved cases from 62.9% to 76.4% (Penicillin 65.7%–78.5% and Cephalosporin from 46.3% to 62.2%).

Unsolved cases were referred to 4 different hospital-based dermatological and 2 paediatric departments in Vienna that perform DPTs. However, due to their limited capacities (see Discussion), only some patients ended up in a DPT (personal communication with the mentioned departments). Unlike in Scandinavian countries or the UK, Austrian has very strict data protection laws that obstructed a structured follow up of these routine patients after leaving our allergy centre. Only a single 52-year-old woman returned to us reporting about her negative DPT.

Predisposing factors

Finally, we looked for predisposing factors for positive or negative outcomes (Fig. 6). For this analysis, we only considered patients where the algorithm resulted in a clear yes/no situation (according to Fig. 5). Two factors reached significance:

1. Male (40%) > female sex (29.5%) ($p = 0.0012$, χ^2 test). This was remarkable as the number of female patients with a referral history for DHR was 2.54 times higher than the one of males (Table 1).
2. Age <11: Younger children carried a lower risk for a confirmation of the DHR, than the older study population >10 years ($p = 0.0411$, χ^2 -test).

All other studied factors shown in Figure 6 such as parental history for a DHR in childhood, underlying atopy or chronic urticaria, a history suggestive for an immediate or a delayed reaction pattern did not differ significantly between confirmed and disapproved cases.

In a previous study, we had reported elevated serum tryptase levels as a risk factor for severe DHR.³² In contrast, this time elevated serum tryptase of ≥ 11.4 ng/ml was only detectable in 17/447 (3.8%) and only one of these patients had a confirmed reaction.

Discussion

Recently, voices in the allergy community have been advocating a turn away from the classical approach including skin and *in vitro* tests prior to a DPT. Instead, they favour a direct DPT without prior testing, which has been propagated especially in North America.^{12,20,21,23} With our study, we would like to stress the point, that aiming for such an extreme standpoint puts patients at unnecessary risks while roughly a third of DHR cases can be solved before a DPT is required.

It may be argued that looking at sIgE and skin tests to β -lactams separately, their low positivity rates may lead to the conclusion that they could be dispensable.²³ Rightly, the low rate of 4.3% drug-specific IgE to β -lactams on the ImmunoCAP® system of this study nearly replicated the 3.4% we had already described 14 years ago.³³ However, these tests are cheap and can be easily applied on large patient groups.¹³ Tweaking read out parameters such as lowering the threshold to 0.1 kU/l could have doubled or calculating



Fig. 6. Risk factor analysis. Risk factor analysis for a confirmation (● red) of the drug hypersensitivity reaction (DHR) versus its disapproval (● green). Women and younger children had a significantly lower risk for a confirmed DHR than men and teenagers/adults. This analysis included only the 346 solved cases according to Fig. 1 and 5. Significance was calculated using a χ^2 -test.

slgE/total IgE ratios could have even quadrupled the positivity rates in our patients, but this would have come at the price of a lowered specificity.²⁹ Basophil activation tests are reported as having superior sensitivity and specificity.^{34,35} However, they consume expensive raw materials and laboratory equipment, require especially trained personnel, and the costs are not covered by health insurances in Austria and some other countries. This restricts them to limited number of patients and hampers their use on broader routine dimensions. Lymphocyte transformation tests seem to have a value in severe cutaneous adverse reactions¹⁴ but there were only two of them in our study population.

Our study underlines the role of skin testing and we performed them successfully even in 98 children ≤ 10 years. Positive skin tests in our study occurred nearly in twice as many patients (7.8%) as drug-slgE (4.3%). This confirms that skin tests are more sensitive than blood tests with a high specificity and a good negative predictive value.³⁶ However, also skin test-specificity had been challenged³⁷ and single cases of false positive tests to Penicillin G had been reported.³⁶ Other studies confirmed a high specificity of IDTs to penicillins³⁸ and cephalosporins.³⁹

IDTs with early and late readings are the most useful skin tests in the workup of DHR. They cause a little bit of pain, which is usually well tolerated even by young patients, and they are safe as we experienced no systemic reaction in 1697 IDTs. When a late reading of the IDT is available, PTs added only little additional value and might be omitted in the routine setting. Still, PTs to β -lactams may have a role in the history of severe cutaneous adverse reactions or in other situations, where IDTs are impossible due to patient-specific factors.

Interestingly, the higher rate of confirmed reactions to cephalosporins was just based on the immediate reaction pattern. This had already been described by Romano *et al.* who confirmed a lot of immediate but hardly any delayed type reactions by skin testing.⁴⁰

DPTs are the golden standard to rule out or confirm a DHR.^{19,41} This is especially true for the non-immunologically mediated reactions to non-steroidal anti-inflammatory drugs.⁴² While representing the gold-standard, they are not perfect tests. Numerous studies described false-positive^{33,43} and false-negative reactions.⁴⁴ DPTs put patients at risks, are an expensive and resource-consuming measure and are a limited resource, even in well-developed health care systems. In Austria, one of the top-ten countries concerning access to public healthcare,⁴⁵ there is currently no reimbursement scheme for DPTs neither by public nor private healthcare insurances. Because of this lacking financial incentive for hospitals and outpatient facilities, Austria is faced with scarce resources for performing DPTs. For example, the metropolitan area of the Austrian capital city Vienna counts around 3 million inhabitants. Four dermatological and two paediatric wards are the only institutions offering DPTs with a long waiting list. A personal communication with these institutions revealed a capacity of around 465 DPTs/year. The majority of these (300) are offered by the dermatological department at the Medical University of Vienna. In an own older study at this institution,³³ only 44.7% provocation tests were reserved for antibiotics, the rest for other drugs e.g. NSAIDs and foods. Assuming, that this ratio has not changed much over time, the yearly capacity for performing DPTs with antibiotics in greater Vienna can be estimated at roughly 200/year. Of the 932 patients in our 2-year study, 37.1% of the cases were solved by the diagnostic algorithm with a clear yes/no outcome. While these 346 individuals already received an allergy passport³¹ or the instruction that they can safely re-introduce β -lactams in their antibiotic regimen, the majority of 62.9% cases remained unresolved with an ongoing need for DPTs. These 586 patients/2 years (=269/year) of our single allergy outpatient clinic alone, would have greatly overwhelmed all DPT capacities of Eastern

Austria. To top the ante, there are 4 additional Viennese allergy outpatient clinics and many more specialists for dermatology and paediatrics who see additional cases. Hence, the full conventional allergy workup of an allergy outpatient clinic is required to reduce the pressure on the bottleneck of DPT capacities.

Many more female patients are seeking help concerning a presumed "penicillin allergy" than men. This is visible in Table 1 (669 = 72% females = and 263 = 28% males) which is in accordance with published data in drug hypersensitivity.^{46–48} We think that this over-representation of female patients is caused by a reporting bias. Gender-specific, higher ratios of positive allergy tests in males than females were described in a recent Chinese study for inhalative and nutritive allergens.⁴⁹

Viral infections inducing life-long immunity for e.g. Herpes viruses such as EBV, CMV etc. happen in early life. Many of these primary viral infections can be accompanied by unspecific exanthemas that may be quite frequently confused with a maculopapular drug rash to an accompanying antibiotic treatment. We think that this mix-up of viral and pseudo drug exanthema explains a higher rate of false histories for delayed drug reactions to penicillins in children than in adults resulting in a lower rate of positive tests in younger children.

Conclusion

We believe that the combination of easy and cheap methods, each of limited sensitivity in a conventional DHR workup as recommended by many international and national guidelines^{3,16,17} is still required for an efficient management of unevaluated DHRs to β -lactam antibiotics. Relying on DPTs alone overstrains most healthcare systems.

Acknowledgements

We are indebted to the following specialists for sharing their information about capacities for performing DPTs at their Vienna-based institutions with us: Christine Bangert MD (Department of Dermatology, Medical University of Vienna, Austria), Detlev Pirkhammer MD (Department of Dermatology and Venereology, "Klinik Landstraße"), Paul Sator MD (Department of Dermatology, "Klinik Hietzing"), Arno Seeber MD (Department of Dermatology, "Klinik Donaustadt"), Zsolt Szépfalusi MD (Department of Pediatrics and Adolescent Medicine, Medical University of Vienna).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.09.010>.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

SW conceived the study, supervised CO during his medical diploma thesis, took care of the patients, analysed the data, and wrote the manuscript. CO collected the data during a chart review of all cases in course of his medical diploma thesis at the Medical University of Vienna. GSG, RJ and FW took care of the patients and proof-read the manuscript. WH co-analysed the data and supported in writing the manuscript. All authors read and approved the final manuscript.

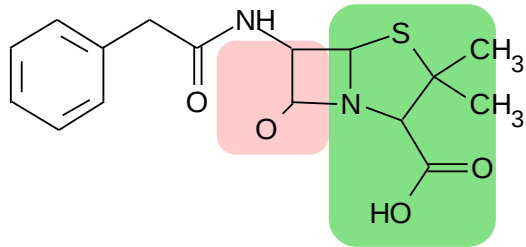
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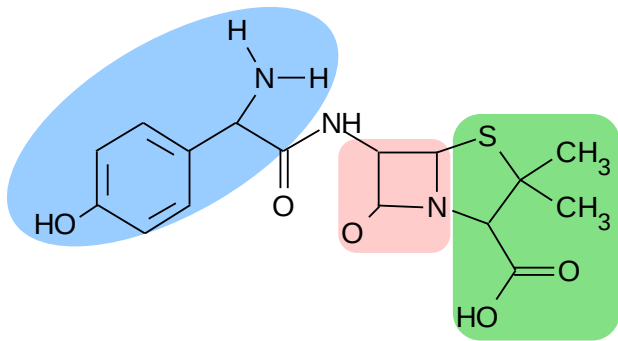
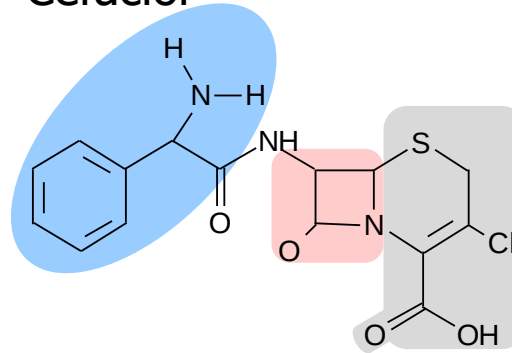
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Supplementary Fig. 1. Chemical structure of β -lactam and cephalosporin antibiotics

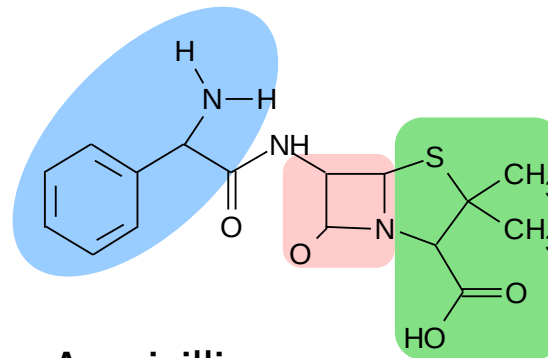
Penicillin G



Cefaclor



Amoxicillin



Ampicillin

Cross-reactivity in penicillins and cephalosporins is caused by similarities in the chemical structure of the drugs, which share their common β -lactam ring structure (● light pink). That is why they are known as “ β -lactam” antibiotics. The thiazolidine ring of penicillins (● light green) differentiates them from the dihydrothiazine ring of cephalosporins (● light grey). Cefaclor and ampicillin share their acyl side chain, and the one of amoxicillin is also rather similar (● light blue).

Pictures were drawn according to Blumenthal KG et al. Antibiotic allergy. Lancet. 2019;393(10167):183-98, and Zagursky RJ et al. Cross-reactivity in beta-lactam allergy. J Allergy Clin Immunol Pract. 2018;6(1):72-81. e1.