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INVESTIGATIVE REPORT

One-week Oral Challenge with Penicillin in Diagnosis of Penicillin Allergy

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Many patients experience reactions during penicillin treatment. The diagnosis may be difficult and is mainly based on short-term tests. The European Network for Drug Allergy (ENDA) guidelines proposed for diagnosing penicillin allergy do not include long-term challenge. In this study a total of 405 patients were evaluated. The ENDA guidelines were extended, to include a 7-day oral treatment (p.o.7) with penicillin for all patients who were negative in the ENDA programme. Among the 405 patients; 85 had an immediate reaction to penicillin, and a further 13 reacted during p.o.7. Among the 307 patients with a negative outcome, 88 had a case history of reaction to other β-lactam antibiotics and were subsequently tested with the culprit drug. Thirteen patients had a positive outcome: 3 on single-dose challenge and 10 during p.o.7. The extended penicillin diagnostic work-up was positive in 111 patients, 30.0% showed immediate reactions and 5.7% reacted during p.o.7. Approximately 20% of all patients with positive outcome during penicillin challenge are detected by adding p.o.7 with penicillin to the original ENDA guidelines. ***Key words: ENDA guidelines; one week challenge; penicillin allergy.***

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The diagnosis of immediate allergic reactions to β-lactam antibiotics is based on the European Network for Drug Allergy (ENDA) guidelines (1). Non-immediate manifestations, particularly maculopapular eruptions, are common during β-lactam treatment. Patch test, delayed-reading intradermal testing and lymphocyte transformation test have been suggested in the diagnostic work-up of non-immediate reactions, followed by intravenous and oral challenge in negative cases. However, a systematic evaluation of the diagnostic work-up of penicillin allergy according to ENDA guidelines supplemented with (when negative), evaluation with prolonged oral treatment with penicillin has been published only in a preliminary study from our group (2).

MATERIALS AND METHODS

Patient selection

At the Allergy Centre, Odense University Hospital, Denmark, a total of 405 adult patients (278 women (68.6%) and 127 men (31.4%)) with a history of hypersensitivity reactions to β-lactam antibiotics were evaluated during the period 2007 to 2009. Penicillin was the culprit drug in 72% of the case histories. The mean age of the females was 46 years (range 16–88 years) and, of males, 45 years (range 16–87 years). In 12.1% of patients the reported time interval between the initial reaction and investigation was less than one year, 12.1% between one and 5 years, and 10.4% more than 5 years, whereas 65.4% did not recall the time of reaction. The reported symptoms were almost exclusively cutaneous, mainly urticaria ($n = 144$), angioedema ($n = 30$) and unclassified cutaneous rash (UCR) ($n = 182$). Anaphylaxis was reported by nine patients, whereas 37 did not recall the nature of their initial reaction. Three patients had other symptoms.

Diagnostic work-up

All patients were investigated according to the ENDA guidelines (1), except using the penicillins for intracutaneous test (ICT) at a concentration of 1.25 mg/ml, because false positive reactions were seen using higher concentrations (3). If the ENDA programme proved negative, the investigations continued with a prolonged oral (7 day) treatment (p.o.7) with penicillin.

On the first and second evaluation days, case history, clinical examination, specific IgE-antibodies against penicillin, standard prick test (SPT) and ICT were carried out (Part A).

The ICT was carried out only if SPT was negative. On day 3 all patients with negative results underwent penicillin challenge (see below: Penicillin challenge (part B)) and the extended protocol.

IgE analysis (part A)

Specific IgE-antibodies against penicillin V, G, ampicillin and amoxicillin were measured using CAP-FEIA® (Phadia, Uppsala, Sweden).

Skin testing (part A)

SPT with benzylpenicillin, ampicillin and amoxicillin (1.25 mg/ml) was performed together with SPT with the culprit drug according to patient case history, Histamine 10 mg/ml (ALK-Abello, Hørsholm, Denmark) and isotonic sodium chloride were used as controls. ICT was carried out with benzylpenicillin and ampicillin (1.25 mg/ml). Freshly prepared penicillins diluted with saline were used for SPT and ICT. SPT and ICT were performed on the volar forearm and read after 20 min. SPT wheal's largest diameter > 3 mm was considered positive. ICT was performed by injection of 0.05 ml of each hapten and was considered positive if the wheal's largest diameter was greater than the diameter of the immediate injection papule and accompanied by erythema, concordant with international guidelines (4–7).

Penicillin challenge (part B)

The challenges were performed under anaphylaxis surveillance. The procedure was divided into the following consecutive steps:

- Intravenous challenge with benzylpenicillin. The initial dose was 100 IE followed by 1,000, 10,000, 100,000 and 1,000,000 IU at 20 min interval. Challenge was stopped when a clinical reaction occurred.
- If negative, an oral challenge with 400 mg of phenoxymethylpenicillin was administered 20 min after the last intravenous injection and the patient was observed in the clinic for a further 2 h.
- If negative, the patient was treated at home with a prolonged oral treatment (p.o.7), consisting of 800 mg phenoxymethylpenicillin 3 times a day for 7 days.

Challenge with other culprit drugs (part C)

All the 405 patients participated in parts A and B. Case histories of reactions to other β-lactam antibiotics were seen in 88 patients, and they were subsequently challenged with the culprit drug, initially in a single p.o. challenge protocol, followed by a 7-day repeated p.o with the culprit drug (initial dose: amoxicillin, ampicillin and dicloxacillin 500 mg, followed by p.o.7: 500 mg twice a day (amoxicillin and ampicillin), and dicloxacillin 500 mg three times a day).

Statistical analysis

Statistical analyses were performed using Fisher's exact test. The significance level was set at 5%.

RESULTS

The algorithm of the diagnostic work-up of the 405 patients and the outcome of the allergy tests are described in Fig. 1a.

Part A

Forty-four of the 405 patients were IgE-sensitized to penicillin and one was positive in SPT.

ICT was performed in the remaining 360 patients and was positive in 20 patients. The remaining 340 patients were subsequently challenged with penicillin (part B) according to Fig. 1a (1, 8, 9).

Part B

During i.v. challenge 5 patients were positive; the remaining 335 received oral challenge (single dose) with phenoxymethylpenicillin, where 15 proved positive. The remaining 320 patients received a prolonged oral (7 day) treatment with phenoxymethylpenicillin (p.o.7); 13 had a positive reaction.

Part C

In parts A and B 307 patients had a negative outcome. Among these, 88 had a case history of reactions to other β-lactam antibiotics and were subsequently

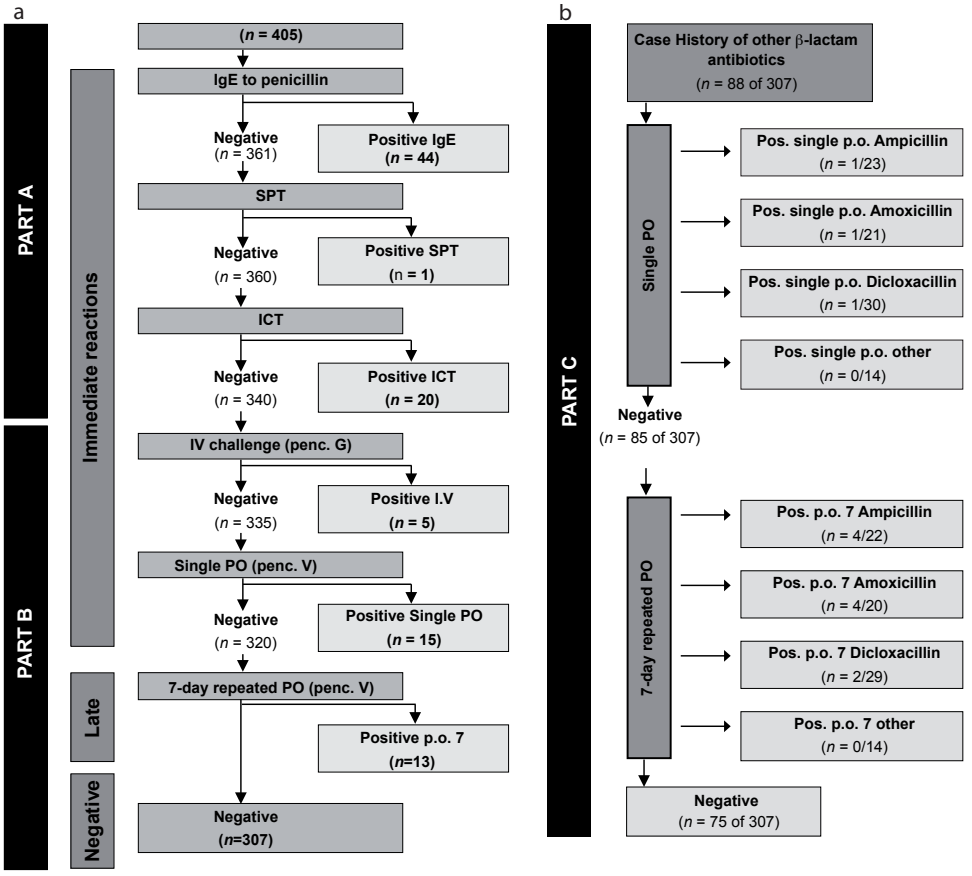

Fig. 1. Diagnostic work-up for penicillin allergy at the Allergy Centre, Odense University Hospital in the period 2007 to 2009. (a) Parts A and B. (b) Part C. Other β-lactam antibiotics (including meropenem, cefuroxime and pivmecillinam). IV: intravenous; PO: oral; p.o.7: 7-day oral treatment with penicillin; IgE: immunoglobulin E; SPT: standard prick test; ICT: intracutaneous test.

Table I. *Patterns of IgE sensitization and skin testing. Dicloxacillin was included only in cases (n = 30) with dicloxacillin as the culprit drug*

	Penicillin G	Ampicillin	Amoxicillin	Dicloxacillin	Penicillin G + Ampicillin	Ampicillin + Amoxicillin	Penicillin G + Ampicillin + Amoxicillin	Ampicillin + Dicloxacillin	Penicillin V alone
	n	*n*	*n*	*n*	*n*	*n*	*n*	*n*	*n*
Part A. Positive reactions in IgE, SPT and ICT									
IgE (n = 44)									
Penicillin V positive	8	1	0	nd	4	1	3	nd	17
Penicillin V negative	0	10	0	nd	0	0	0	nd	
SPT (n = 1)	1	0	0	nd					
ICT (n = 20)	5	9	nd	2	3			1	

nd: not done; IgE: immunoglobulin E; SPT: standard prick test; ICT: intracutaneous test.

Table II. *Relationship between case history and penicillin challenge with respect to type of reaction. Grey cells indicate concordance of type of reactions eliciting primary reaction and challenge*

	Case history								
	i.v/p.o positive (n=23)					p.o.7 positive (n=23)			
	Urticaria/angioedema	Maculopapulous exanthema	Erythema fixum	Severe gastric symptoms		Urticaria/angioedema	Maculopapulous exanthema	Hand eczema	
	n	*n*	*n*	*n*		*n*	*n*	*n*	
Parts B and C. Challenge									
Urticaria/angioedema	13	2				9	4		
Unclassified cutaneous rash	3	3		1		5	4	1	
Erythema fixum			1						

i.v./p.o.: intravenous/oral; p.o.7: 7-day oral treatment with penicillin.

tested according to Fig. 1b. In all, 13 out of 88 patients with a negative challenge with penicillin were positive to other β-lactam antibiotics.

Fourteen patients were challenged with other culprit drugs and all were negative.

The extended penicillin diagnostic evaluation (parts A, B and C) was positive in 111 patients (27.4%). Out of the 405 patients 88 (21.7%) showed immediate reactions according to the ENDA guidelines. In addition, 23 patients (5.7%) reacted during p.o.7.

Patterns of IgE sensitization

IgE-sensitization to penicillin was demonstrated in 44 patients, where 34 had specific IgE to penicillin V. Mono-sensitization to penicillin V was seen in 17 patients, 15 had specific IgE to both penicillin G and V. IgE-sensitization to ampicillin was found in 19 patients and in 10 cases to ampicillin alone. None had specific IgE to amoxicillin only. Seventeen patients were sensitized to more than one of the four penicillins (Table I).

All patients sensitized to penicillin V and/or penicillin G were treated with penicillin during their primary reaction, except for two cases where the culprit drugs were amoxicillin and cefuroxime, respectively. In the 10 cases with IgE to ampicillin alone only one reported ampicillin as the culprit drug.

Patterns of skin testing

One of 405 patients demonstrated a positive SPT to penicillin G without being IgE sensitized (Table I). Among the 20 patients positive in ICT, 8 reacted to penicillin G, 13 to ampicillin and 3 to dicloxacillin. In 4 cases the patient had a positive reaction to two drugs.

Reactions in challenge positive patients.

Urticaria/angioedema were the most commonly reported reaction both in the 23 patients positive on i.v. or single p.o. challenge and the 23 patients in p.o.7 group.

A high correlation was found between case history and the reactions elicited during challenge (Tables II and III). This was primarily seen in 17 of the 23 patients with immediate reactions (13 cases of urticaria/angioedema, three cases of UCR and one case of erythema fixum), whereas 13 out of 23 reproduced their case history during the p.o.7 (9 cases of urticaria/angioedema and 4 cases of ma-

Table III. *Distribution of symptoms according to case history and diagnostic evaluation*

		Part A ($n=405$)			Parts B ($n=340$) and C ($n=88$)				
Case history symptoms	Total ($n=405$) *n*	IgE positive ($n=44$) *n*	SPT positive ($n=1$) *n*	ICT positive ($n=20$) *n*	i.v. positiv ($n=5$) *n*	p.o. positive ($n=18$) *n*	p.o.7 positive ($n=23$) *n*	Any positive ($n=111$) *n* (%)	Negative ($n=294$) *n* (%)
Anaphylaxis, urticaria, angioedema	185	25	1	13	3	12	13	67 (36.2)	118 (63.8)
Unclassified cutaneous rash, unknown	217	19		6	2	5	10	42 (19.4)	175 (80.6)
Sweet's syndrome	1			1				1 (100)	
Erythema fixum	1					1		1 (100)	
Respiratory symptoms	1								1 (100)

Penicillin was the culprit drug in 72% of the case histories. In 87.4% penicillin was the responsible drug regarding intravenous (i.v.)/oral (p.o.)-positive patients and 56.5% in the subgroup p.o.7 positive. In most cases the other culprit drugs were equally distributed.
p.o.7: 7-day oral treatment with penicillin; IgE: immunoglobulin E; SPT: standard prick test; ICT: intracutaneous test.

culopapulous rash. No significant difference was found between the two subgroups ($p>0.05$).

Ninety-one of the 111 patients with a positive challenge remembered the nature and timing of their initial reaction. This finding is in contrast to the negative patients, where only 48 of 294 patients could describe their initial reaction ($p<0.05$). Patients with a case history of anaphylaxis, urticaria or angioedema were significantly more likely to be positive in the tests (part A, B or C) than patients reporting UCR or those not remembering the nature of their initial reaction (36.2% vs. 19.4% positive) ($p<0.05$) (Table III).

Penicillin was the responsible drug in 20 of the 23 patients positive in either i.v. or single-dose p.o. challenge. In all patients except one the culprit drug was identical to the responsible drug during challenge. Thirteen of the 23 patients responding during p.o.7 had a positive reaction to penicillin, the remaining reacting to dicloxacillin ($n=2$), amoxicillin ($n=4$) or ampicillin ($n=4$). In 20 of the 23 patients the culprit drug was identical to the responsible drug during challenge (Table IV).

Time interval between p.o.7 and clinical reaction

The reactions in the 23 patients in most cases appeared later than reported in case history. None of the patients reacted during the first day of p.o.7. The latest day of reaction in case history was day 16. Latest positive challenge was seen at day 10, 3 days after completed p.o.7.

Time interval between self-reported reaction and diagnostic work-up.

The time interval between the allergic reaction during treatment and the diagnostic work-up is illustrated in Fig. 2. Patients with positive IgE to penicillins were found almost exclusively in the group of patients with an initial reaction within a year before the investigation. Patients positive in skin tests or challenge were more evenly distributed, differing significantly from the patients with negative penicillin challenge (83.7%) only rarely remembering the nature and time of their initial reaction ($p<0.05$).

DISCUSSION

The present study includes 405 consecutive patients with a case history of penicillin reaction referred to the Allergy Centre, Odense University Hospital during a 2-year period. All patients were tested according to the ENDA guidelines for hypersensitivity reactions to β-lactam antibiotics and, if negative, a 7-day oral treatment was added.

According to ENDA guidelines 88 were positive (immediate reactions). In addition, 23 patients were

Table IV. *Relationship between case history and penicillin challenge with respect to type of culprit drug. Grey cells indicate concordance of antibiotics eliciting primary reaction and challenge*

	Case history							
	i.v./p.o. positive ($n=23$)				p.o.7 positive ($n=23$)			
	Penicillin *n*	Dicloxacillin *n*	Ampicillin *n*	Amoxicillin *n*	Penicillin *n*	Dicloxacillin *n*	Ampicillin *n*	Amoxicillin *n*
Parts B and C. Challenge								
Penicillin	19				12			1
Dicloxacillin	1	1				2		
Ampicillin			1		1		4	1
Amoxicillin				1				2

i.v./p.o.: intravenous/oral; p.o.7: 7-day oral treatment with penicillin.

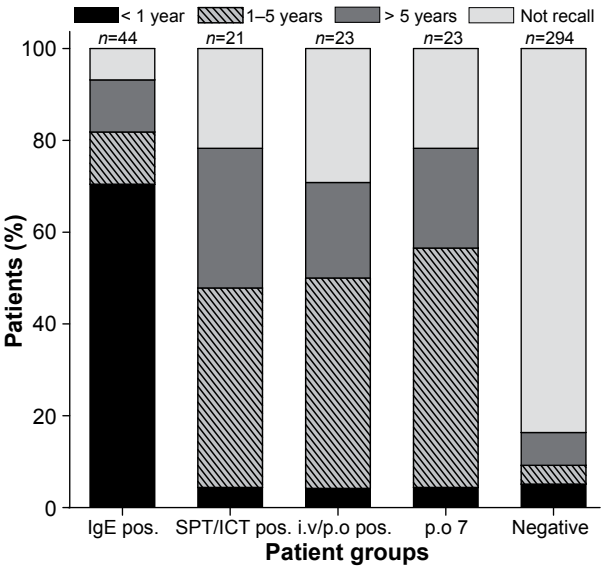

Fig. 2. Time interval between primary reaction and diagnostic work-up at the Allergy Centre according to the five different patient groups. i.v.: intravenous; p.o.: oral; p.o.7: 7-day oral treatment with penicillin; IgE: immunoglobulin E; SPT: standard prick test; ICT: intracutaneous test.

found to develop a reaction during the subsequent 7-day challenge with oral penicillin. This extended penicillin diagnostic work-up thus provides a significant diagnostic improvement. In total, 27.4% of the patients had a positive outcome in our diagnostic evaluation, including the 5.7% having a positive outcome during p.o.7. Two other studies following ENDA guidelines have published similar results (10, 11). In another large study following international guidelines only 8.4% of patients with possible β-lactam allergy were positive during challenge (12). Apart from the fact that children were included in the study by Messaad, there are no obvious reasons for this discrepancy when looking at inclusion criteria, age and sex distribution, diagnostic work-up (excluding p.o.7) or patient case histories. Torres et al. (13, 14) reported an even higher frequency (88%) of a positive outcome, mainly due to positive skin tests. Whether these findings reflect differences in testing procedures (including major and minor penicilloyl determinants) or regional differences are unknown. However, they also show a significant proportion of cases with a clear positive history of immediate allergic reaction and with both negative skin tests and specific IgE to be positive during drug challenge.

Immediate reactions

Hypersensitivity reactions to β-lactam antibiotics are classified as immediate or non-immediate reactions. Previous studies have demonstrated the presence of IgE-antibodies to penicillins in patients with immediate reactions, and the involvement of these antibodies in urticaria, angioedema and anaphylaxis is well known (1, 8, 15). Five of 9 patients with anaphylaxis had positive IgE, but only two proved positive in skin tests (ICT).

None of the 44 patients with IgE-sensitization towards penicillin had a positive skin test, neither SPT nor ICT. In contrast to what is normally observed in patients with type 1 allergy, there is a total lack of correlation between IgE and skin testing. Torres et al. (14) found the same patterns of negative skin tests in patients with IgE-sensitization, reporting 11.5% to be skin test negative and IgE positive. Patients with immediate clinical reactions to β-lactam antibiotics may thus be positive or negative in IgE- and/or skin testing. The reason for this is unknown, but it emphasizes the importance of controlled challenge.

According to ENDA guidelines, skin testing with penicilloyl-polylysine (PPL) and minor determinant mixture (MDM) represents the first-line method for evaluating immediate reactions to β-lactam antibiotics. Because of the unavailability of PPL and MDM in Denmark during this investigation, these penicillin reagents were not used in our evaluation. Skin testing with PPL and MDM in proportion to penicillins has been illustrated by Romano et al. (7). According to their study, skin testing with benzylpenicillin may compensate for PPL and MDM unavailability. Torres et al. (13) found, in a large study, an equal distribution between patients positive in skin testing with benzylpenicillin and MDM.

Time interval

In the present study the time interval between self-reported reaction and diagnostic work-up was important. Most patients with IgE-sensitization are diagnosed within one year, indicating that the level of IgE decreases over time, as has been reported in other studies (1, 8, 9, 16–18). The diagnostic significance of a transient IgE to penicillin is unclear.

Patients should therefore preferentially be examined within one year after the initial reaction.

Predictive factors

Many patients (65.7%) are unable to give a detailed case history, and there is a significant inverse correlation between time interval between the self-reported reaction and the diagnostic work-up.

The nature of symptoms constitutes a statistically significant factor predicting test outcome. If the case history indicates symptoms such as anaphylaxis, angioedema or urticaria there is an increased probability of positive test outcome, in contrast to case histories such as UCR or unknown symptoms. A short time interval between reaction and diagnostic work-up and severity of symptoms indicates a higher hit-rate for establishing a positive outcome. Furthermore, positive patients are found almost exclusively among patients reporting cutaneous symptoms in the case history (all except one,

who had respiratory reactions only). Positive outcome of allergy testing is, however, also seen among the patients with symptoms such as UCR or unknown symptoms. Complete diagnostic evaluation is therefore necessary in each patient.

Patterns of culprit drug

Penicillin was the culprit drug in 72% of the primary reactions. The majority of studies on penicillin allergy in Europe originate from the Mediterranean area, where the distribution of β-lactam use differs from that in the Scandinavian countries.

A European Surveillance of Antimicrobial Consumption (ESAC) project monitored the use of penicillins in 25 countries in Europe, and found that narrow-spectrum penicillin (mainly phenoxymethylpenicillin) represented more than 60% of penicillin use in Scandinavia, whereas narrow-spectrum penicillin represented less than 2% of use the Mediterranean area. Broad-spectrum penicillins (mainly amoxicillin) were most frequently prescribed in the Mediterranean countries (19).

In accordance with their self-reported culprit drug reaction, some patients in our study showed a negative challenge with benzylpenicillin and phenoxymethylpenicillin and a positive challenge with other β-lactam antibiotics. This is in agreement with a previous study indicating that cross-reactivity among penicillins is not a general rule (20).

Among the 23 patients responding during p.o.7, none reacted on day one. It is therefore safe to discharge the patient after a negative challenge with penicillin for use at home for the next 7 days.

ENDA guidelines for investigation of hypersensitivity reactions to β-lactam antibiotics are the gold standard for a definitive diagnosis of penicillin allergy. At its present level of development, however, there is still room for improvement, since we have demonstrated that approximately 20% (23/111 patients) of all the patients with positive outcome on penicillin challenge are detected by including a prolonged oral treatment with penicillin.

The authors declare no conflicts of interest.

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