

Original Article

Reliability of Early and Late Testing for Suspected Perioperative Hypersensitivity

Marie-Line M. van der Poorten, MD^{a,b}, Mark Walschot, MD^a, Margaretha Faber, MD, PhD^a, Jessy Elst, MSc^a, Athina L. Van Gasse, MD, PhD^{a,b}, Leander De Puyseleir, MD^a, Christel M. Mertens, MLT^a, Margo M. Hagendorens, MD, PhD^{a,b}, Lene H. Garvey, MD, PhD^{c,d}, Vito Sabato, MD, PhD^{a,e}, and Didier G. Ebo, MD, PhD^{a,e} *Antwerp and Ghent, Belgium; and Copenhagen, Denmark*

What is already known about this topic? Diagnostic investigation for a perioperative hypersensitivity reaction is thought to be best performed at least 4 to 6 weeks after the event. Some guidelines discourage *in vitro* testing later than 3 years after the index reaction.

What does this article add to our knowledge? This study showed a high proportion of positive skin and *in vitro* tests within 6 weeks after the reaction. For *in vitro* and *ex vivo* tests, sensitivity may decline over time. However, we still found positive tests more than 3 years after the index reaction.

How does this study impact current management guidelines? The study challenges the doctrine that diagnostic workup of perioperative hypersensitivity reactions is best postponed until 6 weeks after the reaction and that *in vitro* and *ex vivo* testing should be discouraged later than 3 years after the event.

BACKGROUND: The optimal timing of diagnostic testing for perioperative hypersensitivity (POH) remains unknown. It has been recommended that investigation is best carried out at least 4 to 6 weeks after the event. On the other hand, guidelines discourage the use of *in vitro* tests later than 3 years after the index reaction.

OBJECTIVE: This retrospective study aimed to assess the reliability of early and late skin tests (STs). It also attempted to verify whether discouraging late *ex vivo* and *in vitro* tests is substantiated.

METHODS: For the first aim, patients were stratified over three epochs: an early timing group, with investigations performed within 6 weeks; a recommended timing group, with tests performed between 6 weeks and 6 months; and a late timing

group, tested later than 6 months after the event. For the second study purpose, we studied the reliability of specific IgE quantification and basophil activation test rocuronium within 6 weeks and after 3 years in patients who experienced an ST-proven POH to rocuronium.

RESULTS: A total of 677 patients were included. Based on a positive ST result, a causative agent was found in 74.2% of the early timing group, 62.6% of the recommended timing group, and 50% of the late timing group. A positive specific IgE for rocuronium or morphine was found in 80% of patients tested within 6 weeks, 63% of patients tested between 6 weeks and 3 years, and 50% of patients tested more than 3 years after the event. A positive basophil activation test was found in 83.3%, 51%, and 20%, respectively, of patients.

CONCLUSIONS: Our data confirm that evaluation of drug allergy for suspected POH can be performed before 6 weeks after the event, and there is no maximal upper time limit disclosing *ex vivo* and *in vitro* testing. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)

Key words: Anaphylaxis; Anesthetic reactions; Drug reactions; Skin testing; sIgE quantification; In vitro diagnostics; Perioperative hypersensitivity

^aFaculty of Medicine and Health Science, Department of Immunology, Allergy, and Rheumatology, Antwerp University Hospital, and the Infla-Med Centre of Excellence, University of Antwerp, Antwerp, Belgium

^bFaculty of Medicine and Health Science, Department of Paediatrics, University of Antwerp, Antwerp University Hospital, Antwerp, Belgium

^cAllergy Clinic, Department of Dermatology and Allergy, Gentofte Hospital, Copenhagen, Denmark

^dDepartment of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

^eDepartment of Immunology and Allergy, AZ Jan Palfijn Gent, Ghent, Belgium
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Corresponding author: Didier G. Ebo, MD, PhD, Laboratory of Immunology, University of Antwerp, CDE T5.95 Universiteitsplein 1, 2610 Antwerp, Belgium.
E-mail: immuno@uantwerpen.be.

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INTRODUCTION

Perioperative hypersensitivity (POH) reactions are complex clinical events with serious consequences resulting from diagnostic error. Correct identification of such reactions by the attending anesthetist and referral to an allergist are mandatory to avoid subsequent reactions. As indicated in a latest European Academy of Allergy and Clinical Immunology (EAACI) position

Abbreviations used

BAT- Basophil activation test
 DC- Drug challenge
 EAACI- European Academy of Allergy and Clinical Immunology
 IDT- Intradermal test
 NMBA- Neuromuscular blocking agent
 NS- Not significant
 POH- Perioperative hypersensitivity
 sIgE- specific IgE
 ST- Skin test
 SPT- Skin prick test

paper¹ investigating suspected POH reactions, the optimal timing for drug allergy evaluation remains unknown. Moreover, the optimal timing for testing might depend on the drug or drug class and the type of investigation.^{1,2} It has been recommended that investigations are best performed at least 6 weeks after the event to avoid false-negative results.³⁻⁵ However, some guidelines suggest that investigations can be performed earlier after the index reaction, especially in cases in which surgery cannot be postponed.⁶ In a recent review on early skin testing after suspected POH reactions, Orihara et al⁷ identified seven cases in which the causative drug (rocuronium [3 cases], cisatracurium [3 cases], chlorhexidine [1 case]) was correctly identified as early as 2 weeks after the event. In 2009, Guttormsen et al⁸ identified suxamethonium-specific IgE (sIgE) antibodies in blood samples collected up to 6 hours after the event; and for other allergens such as chlorhexidine, sIgE was also elevated at the time of reaction with a subsequent decrease upon lack of exposure.⁴ Fernández et al⁹ showed negativization of sIgE and basophil activation tests (BATs) to penicillins 1 year after the event in 72% and 82% of patients, respectively. A more recent longitudinal study by Hjortlund et al¹⁰ confirmed that levels of sIgE to penicillins decrease over time, especially in the absence of new contact with the hapten. Similar observations were made for skin tests (STs) for β -lactam antibiotics,² for BATs with neuromuscular blocking agents (NMBAs),¹¹ and for STs and BATs with dipyrone.¹² Based on these studies, the European Network of Drug Allergy/EAACI Drug Allergy Interest Group Position Paper on *in vitro* testing discouraged the use of drug-sIgE assays and BAT later than 3 years after the index reaction.¹³ This conclusion was made even though negativization over time was absolute in none of those studies.^{2,9,11,12} This retrospective study, which used data from a prior POH dataset published in this Journal in 2019,¹⁴ had two purposes: first, to assess the possibilities of both early and late skin testing; and second, to study the reliability of sIgE quantification and BAT to rocuronium after 3 years in patients who experienced an ST-proven POH to this NMBA.

METHODS**Study population**

For this retrospective observational study, we reanalyzed the dataset on POH reactions as described elsewhere.¹⁴ Briefly, all patients were included through the outpatient clinics of Allergology and Pediatrics of the Antwerp University Hospital and the AZ Jan Palfijn Hospital in Ghent between January 2004 and June 2020.

Patients were enrolled if they experienced a suspected POH reaction and had a complete diagnostic workup including STs for all potential causes. The POH reactions were classified corresponding

to a modified Ring and Messmer classification as used in the Sixth National Audit Project.^{1,15} The local ethics committee approved this study (B3002201316408); patients or their representatives provided informed consent in accordance with the Declaration of Helsinki.

For the primary study aim (assessment of the outcomes of early and late skin testing), patients were stratified into three groups according to predefined time points: an early timing group, in which investigations were performed within 6 weeks after the event; a recommended timing group, in which tests were performed between 6 weeks and 6 months after the suspected POH reaction; and a late timing group, which had a diagnostic workup later than 6 months after the event. In the early timing group, all patients were referred to the allergist for urgent testing. Testing was deemed urgent by the referring anesthetist and surgeon.

To investigate the recommendation not to performed *in-vitro* tests later than 3 years post event, in a separate analysis, we selected all patients who demonstrated a positive ST to rocuronium, tested later than 3 years after the event. In these patients, we studied the outcomes of sIgE assays for rocuronium and morphine (a biomarker for sensitization to tertiary and quaternary substituted ammonium structures^{16,17}) and BAT to rocuronium.

For chlorhexidine and latex, the number of confirmed patients in the different groups was too limited for further robust analyses. For cefazolin, no sIgE assay is commercially available and the traditional CD63-based BAT is known to have low sensitivity.¹⁸

Diagnostic investigations

For a detailed description of the diagnostic approach, the reader is referred elsewhere.¹⁴ In our hospital, it is standard practice to offer every patient with a suspected POH a complete allergy workup for all potential culprits. Briefly, STs were the first step in the diagnostic workup of a suspected POH. Skin prick tests (SPTs) and intradermal tests (IDTs) were performed according to the recommendations of the Société Française d'Anesthésie et de Réanimation¹⁹ at the start of this study in 2004 and were amended according to the updated paper by Mertes et al in 2012.²⁰ In 2019, the EAACI published renewed guidelines for the diagnosis of POH.¹ For cefazolin, a maximal nonirritant concentration of 20 mg/mL was used as proposed by our research group.¹⁸ Briefly, SPTs were performed on the ventral part of the forearm with histamine 10 mg/mL (HAL Allergy Benelux BV, Leiden, the Netherlands) as a positive control and saline buffer solution as a negative control. All administered drugs (and potential cross-reactive structures as well as alleged safe alternatives) as well as latex and chlorhexidine were systematically tested. The SPTs were read after 15 minutes and considered positive when the wheal and flare reaction exceeded 3 mm. Patients with negative SPTs had additional serial dilutions of IDTs. For all tested compounds except NMBAs, IDT responses were considered positive when the wheal and flare equaled or exceeded 5 mm or when the wheal had doubled compared with the injection bleb induced by 0.02 mL of the tested solution. For NMBAs, IDT responses were considered positive when the wheal and flare equaled or exceeded 8 mm or when the wheal had doubled compared with the injection bleb.

Quantification of total and sIgE antibodies were performed using the ImmunoCAP FEIA technique (Phadia Thermo Fisher, Uppsala, Sweden). Decision thresholds for latex, chlorhexidine ethylene oxide, suxamethonium, morphine, gelatin, penicilloyl G, penicilloyl V, ampicilloyl, and amoxicilloyl were set at 0.10 or 0.35 kUA/L, as recommended by the manufacturer. For rocuronium, the cutoff was set at 0.13 kUA/L, which was demonstrated to yield optimal combined sensitivity and specificity.¹⁶

TABLE I. Causative agents at different time points, based on positive skin test results

Category	Early timing	Recommended timing	Late timing	P-value		
				Early vs late	Recommended vs late	Early vs recommended
Range, d	5-42	43-180	181-15,616	—	—	—
Interquartile range	14	63.5	966.75	—	—	—
Median	29	78	382	—	—	—
Non-life-threatening, n (%) [*]	20 (30.3%)	129 (35.7%)	121 (48.4%)	< .05	< .05	NS
Life-threatening, n (%) [*]	46 (69.7%)	232 (64.3%)	129 (51.6%)	< .05	< .05	NS
Cause found, n (%) (n = 400)	49 (74.2)	226 (62.6)	125 (50)	< .001	< .05	NS
			29 (44.6%) [*]			
No cause found, n (%) (n = 277)	17 (25.8)	135 (37.4)	125 (50)	< .05	< .05	NS
			36 (55.4%) [*]			
Causative agent						
NMBA, n (%)	20 (30.3)	104 (28.8)	62 (24.8)	NS	NS	NS
Rocuronium	15 (22.7)	84 (23.3)	48 (19.2)			
Other	5 (7.5)	20 (5.5)	14 (5.6)			
Cefazolin	10 (15.2)	37 (10.2)	11 (4.4)	NS	NS	ND
Chlorhexidine	8 (12.1)	19 (5.3)	6 (2.4)	NS	NS	NS
Latex	5 (7.5)	28 (7.7)	27 (10.8)	NS	NS	NS
Other	6 (9)	38 (10.5)	19 (7.6)	NS	NS	NS
Total, n	66	361	250	—	—	—
			65 [†]			

NS, not significant.

Early timing indicates skin tests were performed within 6 wk after the event. Recommended timing indicates skin tests were performed between 6 wk and 6 mo after suspected perioperative hypersensitivity. Late timing indicates skin tests were performed later than 6 mo after the event.

^{*}Non-life threatening anaphylaxis means a National Audit Project score of 1 or 2; life-threatening anaphylaxis means a National Audit Project score of 3 or 4.[†]Testing after 3 y.

Basophil activation tests. A BAT relies on flow cytometric analysis of activated basophils after stimulation with relevant drugs (mainly different NMBA, latex, chlorhexidine, and antibiotics).²¹ For a description of the BAT protocols, the reader is referred elsewhere.^{18,22-24}

Graded drug challenge. When both STs and sIgEs were negative, a graded drug challenge (DC) for cefazolin up to a cumulative dose of 1 g was performed. No challenges were performed for NMBA, latex, and chlorhexidine.

Revision of anesthetic reports and surgical notes from subsequent surgery. To circumvent the limitations of full-dose provocation tests with NMBA, anesthetics, and opioids, we opted to review the anesthetic reports and surgical notes of subsequent surgery.

RESULTS

For the first part of the study, 677 patients who had STs were included. The STs were performed between 5 days and 43 years after the suspected POH. In 66 patients (9.7%), STs were performed within 6 weeks (42 days) after the event (early timing).

In 361 patients (53.3%), STs were performed between 43 days and 6 months after the event (recommended timing).

In 250 patients (37%), STs were performed later than 6 months after the event for POH (late timing).

There were significantly more patients with life-threatening anaphylaxis (National Audit Project score of 3 or 4) in the early and recommended timing group, compared with the late timing group. No significant difference was found between the early and recommended timing groups.

Table I shows that based on a positive ST, a causative agent was found in 49 of 66 patients in the early timing group (74.2%) and 226 of 361 in the recommended timing group (62.6%). In

the late timing group, a cause was demonstrable in 125 of 250 patients (50%; (Fisher exact test, early vs recommended, 0.69; early vs late, $P = .000$; recommended vs late, $P = .002$). The most common causes were NMBA (most often rocuronium), cefazolin, chlorhexidine, and latex, irrespective of the timing of testing.

More than one cause was found in four of 66 patients (6%), 19 of 361 patients (5.3%), and 10 of 250 patients (4%), respectively, in the three groups. We found no significant difference among the groups (Fisher exact test, P not significant [NS]).

We performed a subgroup analyses on all patients who were tested very early (<4 weeks after the event) and patients who were tested very late (more than 3 years after the event). Of the early tested patients, 31 of 66 were tested within 28 days (4 weeks) after the event. A cause was demonstrable in 19 of 31 patients (61.2%). This is not significantly different from the other groups (Fisher exact test, P NS). Eighteen patients had rocuronium STs within 4 weeks and seven had cefazolin STs within 4 weeks. Other causes were chlorhexidine (four patients) and latex (two patients).

In the separate analysis for patients who were tested later than 3 years after the event, a cause was found in 29 of 65 patients (44.6%).

Subsequently, we analyzed the data for rocuronium and cefazolin, the two most common causes of POH in this series (Table II). We found that 544 patients had STs with rocuronium (80%) and 147 of 544 had a positive test (27%); these were divided into 15 of 55 patients (27.3%) who were tested early (<6 weeks), 84 of 297 patients (28.3%) who were tested at the recommended time, and 48 of 192 patients (25%) who had late testing (more than 6 months; Fisher exact test; P NS).

TABLE II. Skin test responsiveness at different time points in patients with positive skin tests for rocuronium and cefazolin

Testing group	Rocuronium (n = 147)			Cefazolin (n = 58)		
	SPT positive	IDT positive	Total	SPT positive	IDT positive	Total
Early	8 (53.3%)	7 (46.7%)	15	1 (10%)	9 (90%)	10
Recommended	53 (63%)	31 (37%)	84	5 (15.6%)	27 (84.4%)	37
Late	32 (66.7%)	16 (33.3%)	48	0	11 (100%)	11

IDT, intradermal test; SPT, skin prick test.

Early timing indicates skin tests were performed within 6 wk after the event; recommended timing indicates skin tests were performed between 6 wk and 6 mo after suspected perioperative hypersensitivity. Late timing indicates skin tests were performed later than 6 mo after the event.

Furthermore, SPTs for rocuronium were positive in 93 of 147 patients (63%); eight of 15 of those patients (53.3%) were in the early testing group, 53 of 84 (63%) were in the recommended testing group, and 32 of 48 (66.7%) were in the late testing group. The number of positive SPTs was not significantly different from that of patients with positive IDTs. We found no difference in IDT concentrations needed for positivity (Fisher exact test, *P* NS).

To evaluate the reliability of early negative ST results, we revised anesthetic notes and surgical reports from subsequent procedures. For rocuronium, 19 of 40 patients who demonstrated an early negative ST rocuronium underwent one or more surgeries after the diagnostic workup. In 14 of 19 patients, an anesthetic record was available and indicated an uneventful course. However, only five patients were reexposed to rocuronium; the remainder had an alternative benzylisoquinoline NMBA. These notes also showed that 26 of 29 patients who had negative STs for propofol were reexposed. For latex and chlorhexidine, 27 of 57 and 29 of 52 patients with negative early STs were reexposed. Moreover, 20 of 29 patients with negative early STs for alfentanil, sufentanil, and fentanyl were reexposed to one or more of these opioids. All reexposures were uneventful.

Data for the reexposed patients are shown in Table E1 (in this article's Online Repository at www.jaci-inpractice.org). Nine of 66 patients who received early testing (13.6%) were reexposed to all tested culprits.

For cefazolin, a positive ST was found in 10 of 22 (45.5%), 37 of 85 (43.5%), and 11 of 38 (29%) patients from the early, recommended, and late timing groups, respectively (Fisher exact test, *P* NS). Most STs were only positive in the IDT. This was the case for nine of 10 patients (90%) who were tested early, 27 of 37 (84.4%) in the recommended group, and all 11 (100%) who were tested later (Fisher exact test, *P* NS).

In the early timing group, 11 of 12 patients with negative STs had a DC for cefazolin; all DCs were negative. In the recommended timing group, DCs for cefazolin were performed in 28 of 48 patients with negative STs. All were negative except one. In the late timing group, DCs were performed in 14 of 27 patients who had a negative ST; only one was positive.

For the second part of our study, we attempted to assess the possibility of early (<6 weeks) or late (more than 3 years) *in vitro* and *ex vivo* testing. Thus, we analyzed 147 patients with hypersensitivity to rocuronium confirmed by positive STs. For chlorhexidine and latex, the number of confirmed patients in the different groups was too limited for further robust analyses. For cefazolin, no sIgE assay is commercially available, and traditional CD63-based BAT is known to have low sensitivity.¹⁸

For all 147 patients, an sIgE result for rocuronium and morphine (a biomarker for sensitization to tertiary and

quaternary substituted ammonium structures^{16,17}) was available. Fifteen patients were tested within 6 weeks (10.2%), 122 between 6 weeks (42 days) and 3 years (83%), and 10 later than 3 years after the event (6.8%). A positive sIgE for one of the two tested compounds was found in 12 of 15 (80%), 76 of 122 (63%), and five of 10 (50%) patients, respectively (Fisher exact test, *P* NS).

In 134 patients with a positive ST for rocuronium, a BAT rocuronium result was available. We further excluded 15 patients with nonresponding BAT (11%), that is, patients in whom cells did not react to the positive control or antigen; this resulted in 119 patients. Thirteen patients were tested early (10.9%), 96 were tested at the recommended time (80.7%), and 10 were tested late (8.4%) (ie, more than 3 years after the event). A positive BAT was found in 10 of 12 patients (83.3%) and 49 of 96 patients (51%) and only two of 10 patients (20%), respectively (Fisher exact test, late vs early *P* < .05; late vs recommended *P* NS).

We found a positive sIgE for one of the two compounds 12 of 15 patients (80%), 76 of 122 patients (63%), and five of 10 patients (50%), respectively (Fisher exact test, *P* NS).

In 134 patients with a positive rocuronium ST, a BAT rocuronium result was available. We excluded 15 patients with non-responding BAT (11%), that is, patients in whom cells did not react to the positive control or antigen; this resulted in 119 patients. Twelve patients were tested early (10.1%), 96 were tested at the recommended time (80.7%), and 10 were tested late (ie, more than 3 years after the event) (8.4%). A positive BAT was found in 10 of 12 patients (83.3%) 49 of 96 patients (51%), and only two of 10 patients (20%) patients, respectively (Fisher exact test, late vs early *P* < .05; late vs recommended *P* NS).

DISCUSSION

The optimal timing for diagnostic investigation of suspected POH remains unknown. The current doctrine is that false negatives are more common in the first 6 weeks, or with overly delayed testing. Therefore, it has been recommended that testing best takes place between 6 weeks and 6 months after the event.^{3,4} However, knowledge is limited about the early dynamics of serum sIgE titers and refractoriness of effector cells to many of the compounds used during anesthesia. Our rates of cases with positive STs from 677 patients referred to our clinic, challenge a too generic recommendation to delay investigations for 4 to 6 weeks. We found a high proportion of both positive STs and *in vitro* tests within 6 weeks after the reaction and even within 4 weeks after the event. Moreover, the percentage of patients in whom multiple causes were found, was similar in all three groups; hence, early testing does not seem to miss these rare cases.

Consequently, it may not be necessary to postpone drug allergy evaluation, especially in patients who need urgent rescheduling. In contrast, a culprit was less often identifiable in patients who were tested after 6 months. Thus, early investigations do not impede the correct identification of the causative agent(s) and do not compromise correct diagnosis. Admittedly, we cannot completely exclude that patients who experienced severe anaphylaxis were urgently referred for allergy workup, which increased the number of positive tests in the early testing group. On the other hand, if this assumption is true, early STs in these patients can be performed and show good sensitivity.

The optimal timing of testing could depend on the drug or drug class and type of diagnostic investigation. Our findings show that STs for rocuronium and cefazolin can remain positive for many years after the event. Furthermore, although sensitivity was shown to decline over time in *in vitro* and *ex vivo* tests,⁹⁻¹² we confirm that this observation might not apply to all drugs and found that diagnostics for rocuronium remained positive for many years. In patients with positive rocuronium STs more than 3 years after the event, half demonstrated positive sIgE morphine and/or rocuronium results and one-fifth had positive BAT results. Consequently, as indicated by the recent EAACI position paper on investigations into POH,¹ the interval elapsed since the reaction should never preclude a referral and diagnostic workup.

Some inevitable restrictions and limitations should be considered when interpreting the current data. First, as indicated, the lower proportion of positive tests in patients tested after 6 months may have occurred because fewer of those patients experienced a genuine hypersensitivity reaction, or because performance of the tests depends on the severity grade of the reaction. However, even if this were the case, the data, especially for cefazolin patients confirmed by a DC, show that these patients can be tested without false-negative results.

Nevertheless, we think that these data are valid. For cefazolin, we performed challenges in most patients with negative STs, and almost all these DCs were negative irrespective of the timing of testing. Data from an analysis of subsequent anesthesia showed that patients were uneventfully exposed to latex, chlorhexidine, and propofol. Regarding NMBAs, for which DCs are rarely considered, we cannot draw a definite conclusion. Anesthesiologists frequently substitute the index compound with a drug from another class, irrespective of the time of testing.²⁵ However, the negative predictive value of NMBA STs appears to be high.^{25,26}

For *in vitro* and *ex vivo* testing, the same limitations apply to this study. However, positive *in vitro* and *ex vivo* tests were observed in the group with late testing. Hence, we believe that the generalized recommendation not to offer *in vitro* and *ex vivo* tests 3 years after the event is too radical. Nevertheless, when delayed testing is negative, negativization of test results cannot be excluded.

A second limitation of this study relates to its cross-sectional design, which does not allow the longitudinal effect of time on different diagnostics to be explored. To answer this question with certainty would have required a follow-up study with repeated analyses over a long period in a large cohort of patients to enable robust analysis. Here, no repeated testing was performed in patients who tested negative early after the event.

Follow-up of the dynamics of sensitivity of our diagnostics should consider the possibility of new sensitizations that might be extremely difficult to identify, if they are indeed possible, for

drugs such as rocuronium and cefazolin. After all, the sensitization route(s) for these drugs is still obscure, but rocuronium sensitization could be maintained by using pholcodine.¹⁷ Hence, our findings may not necessarily be extrapolated to other drugs; further research is needed to verify these results.

A third consideration is the relevance of these findings for the anesthetist who is faced with a patient with POH. A typical scenario is the patient whose urgent surgery is abandoned because of a suspected POH. The data presented here suggest that tests can be reliable within 6 weeks of an abandoned procedure, enabling early rescheduling. However, a high negative predictive value is essential to avoid a false-negative test leading to a renewed reaction upon reexposure. Therefore, additional, larger studies of several drug groups are required to confirm this observation. Alternatively, these data were obtained from a large dataset and cover a significant period of time, which we think adds to the validity of observations and might shift paradigms about the optimal timing of diagnostics in POH. If necessary, it seems feasible to perform diagnostic testing earlier than 6 weeks after the event. Obviously, when early testing is negative, repeated testing is advised, including a DC if possible.

This study is a reanalysis of a large dataset of 677 patients investigated for suspected POH; it explored the impact of timing on the outcome of the diagnostic workup. The data confirm that drug allergy evaluation for suspected POH does not necessitate a delay for 6 weeks after the event.¹ In cases requiring urgent rescheduling, early testing might be reliable and beneficial. The confirmation that both sIgE and BAT rocuronium can remain positive for many years suggests that *in vitro* and *ex vivo* tests may remain useful for some drug groups despite the current recommendation not to perform *in vitro* tests later than 3 years after the reaction.¹³

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ONLINE REPOSITORY

TABLE E1. Reexposure of different culprits in patients tested less than 6 wk after event

Patient	Re-exposure during subsequent surgery				
	Rocuronium	Propofol	Latex	Chlorhexidine	Opioids
1	Uneventful	Uneventful	Uneventful	No (positive ST)	Uneventful
2	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful
3	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful
4	No	Uneventful	No (positive ST)	Uneventful	Uneventful
5	No	Uneventful	Uneventful	Uneventful	Uneventful
6	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful
7	No	Uneventful	Uneventful	Uneventful	Uneventful
8	No	Uneventful	Uneventful	Uneventful	Uneventful
9	No	Uneventful	Uneventful	Uneventful	No
10	No	Uneventful	Uneventful	Uneventful	No
11	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful
12	No	Uneventful	Uneventful	Uneventful	No
13	No	Uneventful	Uneventful	Uneventful	No
14	No	No	No	No	No
15	No	No	No	No	No
16	No	No (positive ST)	No	No	No
17	No	No	No	No (positive ST)	No
18	No	No	No (positive ST)	No	No
19	No	No	No	No (positive ST)	No
20	No	No	No	No	No
21	No	No	No	No	No
22	No	No	No	No	No
23	No	No	No	No	No
24	No	No	No	No	No
25	No	No	No	No	No
26	No	No	No	No	No
27	No	No	No	No	No
28	No	No	No	No	No
29	No	No	No (positive ST)	No	No
30	No	No	No	No	No
31	No	No	No	No	No
32	No	No	No	No (positive ST)	No
33	No	No	Uneventful	Uneventful	No
34	No	No	No	No	No
35	No	Uneventful	Uneventful	Uneventful	Uneventful
36	No	No	Uneventful	No (positive ST)	No
37	No	No	Uneventful	Uneventful	No
38	No	No	No (positive ST)	No	No
39	No	No	No	No	No
40	No	Uneventful	Uneventful	Uneventful	No
41	No	Uneventful	Uneventful	No (positive ST)	Uneventful
42	No	No	No	No	No
43	No	No	No	No	No
44	No	No	No	No (positive ST)	No
45	No	No	No	No	No
46	No	Uneventful	Uneventful	Uneventful	Uneventful
47	No	Uneventful	Uneventful	Uneventful	Uneventful
48	No	No	No	Uneventful	No
49	No	Uneventful	No (positive ST)	Uneventful	Uneventful
50	No	No	No	No	No

(continued)

TABLE E1. (Continued)

Patient	Re-exposure during subsequent surgery				
	Rocuronium	Propofol	Latex	Chlorhexidine	Opioids
51	No	No	Uneventful	Uneventful	No
52	No (positive ST)	No	No	Uneventful	No
53	No (positive ST)	No	No	No	No
54	No (positive ST)	Uneventful	Uneventful	Uneventful	Uneventful
55	No (positive ST)	No	No	No	No
56	No (positive ST)	No	No	No	No
57	No (positive ST)	Uneventful	Uneventful	Uneventful	Uneventful
58	No (positive ST)	Uneventful	Uneventful	Uneventful	Uneventful
59	No (positive ST)	No	No	Uneventful	No
60	No (positive ST)	Uneventful	Uneventful	Uneventful	Uneventful
61	No (positive ST)	No	No	No	No
62	No (positive ST)	Uneventful	Uneventful	Uneventful	Uneventful
63	No (positive ST)	No	No	No	No
64	No (positive ST)	Uneventful	No	No (positive ST)	No
65	No (positive ST)	Uneventful	No	Uneventful	Uneventful
66	No (positive ST)	No	No	No	No

ST, skin test.

All patients who were reexposed to a drug received a workup for this potential culprit. This included total IgE and specific IgE quantification for latex, chlorhexidine, rocuronium, morphine, and pholcodine (the latter two are reliable biomarkers to depict sensitization to substituted tertiary and quaternary ammonium structures^{E1}). Skin tests for rocuronium, latex, chlorhexidine, propofol, and opioids were also performed. Nine of 66 patients who received early testing were reexposed to all potential culprits (13.6%); hence, they can be considered to have undergone a complete allergy workup.

REFERENCE

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