Acute Management, diagnosis, and follow-up of suspected perioperative hypersensitivity reactions in Flanders 2001-2018

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The authors declare no conflict of interest.

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Abstract

Background: Despite numerous efforts to describe the clinical manifestations and the epidemiology of perioperative hypersensitivity (POH), there remains room to increase awareness among anesthetists and immunologists/allergists.

Objective: To report the findings of a 17-year survey of suspected POH in Antwerp (Belgium).

Methods: We analyzed clinical and diagnostic data from 715 patients referred because of a suspected POH reaction, between January 1, 2001 and May 31, 2018. 456 patients demonstrating a POH could be queried about subsequent anesthesia.

Results: 608 cases formed the final dataset; 208 had a non-life-threatening reaction, 400 a life-threatening reaction. In life-threatening reactions, hypotension was predominating. In the non-life-threatening reactions, 83.9% of the patients displayed cutaneous manifestations. In life-threatening reactions, intravenous adrenaline and fluids were administered in respectively 75.7% and 31%, and 41.3% had their intervention abandoned. Mast cell activation (MCA) was mainly, but not exclusively, observed in severe grades but did not predict the mechanistic process nor the culprit. A cause was identified in 77.8% of severe and 48.6% of milder cases. Main culprits are neuromuscular blocking agents, latex, cefazolin and dyes. 156 had uneventful anesthesia, except one patient who was inadvertently re-exposed to hidden chlorhexidine.

Conclusions: This study highlights that there is room for an improved acute management and an optimized diagnostic work-up that should not be restricted to patients with severe reactions and/or showing mast cell activation.

Keywords: epidemiology; allergy; perioperative hypersensitivity; management; diagnosis

Highlights box

What is already known about this topic?

Perioperative hypersensitivity (POH) is a rare condition with serious consequences of diagnostic error. Significant gaps in our knowledge remain regarding clinical manifestations, treatment and causes of POH.

What does this article add to our knowledge?

In life-threatening reactions, intravenous adrenaline and fluids were administered in respectively 75.7% and 31%. Mast cell activation was mainly, but not exclusively, observed in severe grades but did not predict the mechanistic process nor culprit agent.

How does this study impact current management guidelines?

This study highlights that there remains room for an improved acute management and an optimized diagnostic work-up that should certainly not be restricted to patients with severe reactions and/or showing mast cell activation.

Abbreviations

BAT	basophil activation test
BP	blood pressure
CPR	cardiopulmonary resuscitation
DPT	drug provocation test
ECMO	extracorporeal membrane oxygenation
IDT	intradermal test
IV	intravenous
MC	mast cell
MCA	mast cell activation
MRGPRX	mas-related G protein coupled receptor X
NAP6	sixth national audit project
NMBA	neuromuscular blocking agent
POH	perioperative hypersensitivity
SE	standard error
sIgE	specific immunoglobulin E
SPT	skin prick test

Introduction

Perioperative hypersensitivity (POH) is a rare condition with serious consequences of misdiagnosis [1, 2]. However, the POH scene has its own particularities that might hinder recognition, treatment, diagnostic referral/work-up and correct reporting. Anesthetized patients can demonstrate normal variations in vital signs misinterpreted as POH. *Vice versa*, POH can be interpreted as a normal physiologic variation and distract from appropriate management. Furthermore, clinical signs and symptoms not necessarily reflect a hypersensitivity reaction (*e.g.* bronchospasms during difficult intubation). Mucocutaneous signs of POH can also be invisible due to the surgical drapes covering the patient or due the color spectrum of the theater lights. Lungs are not always accessible for auscultation, but bronchospasm can be suspected because of an increase in inspiration pressure. Diagnosis can also be hampered as many substances that can elicit various phenotypically indistinguishable immune and non-immune reactions are administered simultaneously. For example, since the first description by McNeil *et al*, neuromuscular blocking agents (NMBA) have increasingly been suggested to trigger mast cell (MC) degranulation by off-target occupation of the MRGPRX2 (Mas-related G protein coupled receptor X2) receptor [3]. Moreover, some authors have proposed to reclassify NMBA hypersensitivity as non-immune reactions [4-6]. Finally, causes of POH might show geographical differences [7] and changes over time [8, 9], hampering generalization and comparison of epidemiological data and extrapolation of findings about diagnostic test performances. These differences mainly relate to the lack of consensus definitions and a standardized grading system, differences in referral, and absence of a harmonized diagnostic approach [2, 10-12]. To improve management of perioperative anaphylaxis, the Sixth National Audit Project (NAP6) introduced a new classification for POH and a structured method for classifying suspected anaphylactic events [13].

Two epidemiologic studies on the presentation and causes of POH in Flanders have been published [14, 15]. Here we report on the clinics, treatment, outcome and causes of POH. We adopted the same severity grading. However, we judged not to restrict our analysis to life-threatening reactions and patients with acute tryptase measurements, as allergists will encounter less obvious cases more likely to pose a diagnostic challenge. Observations in children and follow-up data are described separately, as there are few data in children [2, 16-19] and limited follow-up studies [17, 20-28].

Materials and methods

Details of the applied methods are provided in the Methods section in this article's Online Repository. Briefly, data of 715 patients referred to our outpatients' clinic because of a suspected POH reaction, between January 1, 2001 and May 31, 2018 were analyzed. POH reactions were graded corresponding the NAP6 scale [13].

Allergic work-up included total IgE, specific IgE (sIgE), baseline tryptase, skin prick tests (SPT), intradermal tests (IDT), basophil activation tests and drug provocation tests (DPT). Table E1 shows the non-reactive skin test concentrations, table E2 displays the diagnostic procedures for the most important causes of POH. Mast cell activation (MCA) was defined as peak tryptase exceeding 1.2x (baseline tryptase) + 2 µg/L [29]. In the presence of MCA, positive confirmatory testing was considered proof of an immune-mediated. In contrast, in patients with MCA but negative diagnostic work-up were considered to have presented a non-immune reaction.

456 patients demonstrating a POH could be queried about subsequent anesthesia. In 156 cases, additional anesthetic/surgical notes were obtained.

Results

As displayed in figure 1, 608 cases formed the POH dataset. 107 were excluded because of insufficient clinical details or not meeting inclusion criteria. In many of them reaction started 2 hours after administration of the possible culprit. In others, a differential diagnosis was made (*e.g.* anxiety, difficult intubation, subcutaneous emphysema, and over dosage). The remainder presented only mild isolated symptoms such as erythema, bronchospasms, lowered tension without biological evidence MCA.

Clinical features and acute management

As summarized in figure 1, 208 cases were classified as non-life-threatening and 400 as life-threatening hypersensitivity/anaphylaxis. As illustrated in figure 2, in life-threatening reactions, hypotension and bronchospasm was present in respectively 96.7% (381/394) and 48.7% (169/347). In non-life-threatening reactions, 83.9% (172/205) of the patients displayed cutaneous manifestations and 29.1% (59/203) angioedema. In life-threatening and non-life-threatening reactions, the clinical presentation and time-of-onset were indistinguishable between different mechanistic processes. In 75.0% (404/539), the reaction started within 30 minutes after induction. Life-threatening reactions started earlier than the milder reactions (χ^2, $p<0.001$). In five cases life-threatening anaphylaxis preceded induction.

As indicated by figure E1 in the Online Repository clinical presentation was more severe in adults (68%) than in children (35%) (χ^2, $p<0.001$). Only one child demonstrated a grade 4.

As shown in figure 3, in life-threatening reactions, intravenous (IV) adrenaline and fluids were administered in 75.7% (212/280) and only 31% (85/274), respectively. In non-life-threatening reactions, 12.7% (16/126) had IV adrenaline and 5.2% (6/116) fluid substitution. Noticeably, 24

patients with a systolic BP < 50 mmHg had no CPR. Surgical intervention was interrupted in 6.0% (11/182) in the non-life-threatening group and 41.3% (121/293) in the life-threatening group.

Mast cell activation (MCA)

An acute tryptase result, measured 1-6 hours after the onset of symptoms, was available in 254 patients (41.1%). More acute tryptase values were available from life-threatening than from non-life-threatening reactions (204/400 vs. 50/208, χ^2, p<0.001). MCA could be calculated in 250 cases (237 out of 568 adults (41.7%) and 13 out of 40 children (32.5%)), as baseline values were missing in 4. MCA was demonstrable in 185 cases. Figure 1 shows that MCA was more frequent in life-threatening than in non-life-threatening reactions (169/201 *vs.* 16/49, χ^2, p<0.001). Importantly, 19 (10.3%) of the patients demonstrating MCA had an acute tryptase < 11.4 µg/L. MCA was more frequent in adults than in children (180/237 (75.9%) *vs.* 5/13 (38.5%), χ^2, p=0.014).

As illustrated in figure 4 mean (standard error, SE) of acute tryptase in life-threatening reactions (41.5 µg/L, SE=3.64) was higher than in non-life-threatening reactions (9.6 µg/L, SE=1.26) (T-test, p<0.001). Baseline tryptase levels did not differ between life-threatening (5.7 µg/L, SE=0.24) and non-life-threatening reactions (5.1 µg/L, SE=0.23).

Figure E4 and E5 in this article's Online Repository show results about MCA and delta tryptase (acute – baseline) in relation to the underlying mechanistic process, that is immune vs non-immune. In immune responses MCA is more frequent (160/185 vs. 30/65, χ^2, p<0.001). However, nor the presence of MCA, nor the magnitude of the acute tryptase, is absolutely predictive for the mechanism that is assumed to be immune mediated according to the results of confirmatory tests.

As exemplified below, in 196 patients no culprit was identifiable. In 60 out of these 196 patients, an acute tryptase result was available and indicated MCA in 25 cases (41.7%). Twenty-three of these patients (92%) had suffered from a life-threatening reaction.

Identified (explained) events

A culprit was identifiable in 412 cases (67.8%), irrespective the clinical presentation and presence or absence of MCA. In 27 (6.5%) cases, a second offender was identified, giving 439 culprits in 412 cases. In life-threatening reactions, 311 patients (77.8%) had their reaction explained *vs.* 101 cases (48.6%) in the non-life-threatening group (χ^2, p<0.001). Predominant culprits in adults and children were NMBA, latex and antibiotics (Figure E2 in the Online Repository). Table E3 of the online repository summarizes the changes over time.

In the group who had a cause identified, a significant female predominance was observed (279 females), except for chlorhexidine allergy (N.=45, 13 females).

Neuromuscular blocking agents (NMBA)

NMBA predominated POH reactions accounting for 182 of the explained reactions (182/439; 41.5%). From NMBA reactors, 161 (88.5%) suffered from life-threatening reactions. Figure E3 in the Online repository displays the distribution of sensitization to the NMBA.

Reactions to NMBA occurred within 30 minutes after administration, except 4. MCA was present in 82/92 NMBA cases.

In 123 patients with rocuronium allergy who had triple diagnostic tests [30], diagnosis was confirmed by skin tests (ST) and at least one *in vitro* test in 93 (75.6%). Nine patients with negative STs had their diagnosis documented by BAT and sIgE or BAT. In 11 patients with suxamethonium allergy, ST and at least one in vitro test confirmed diagnosis in 9 (81.8%). In 10 atracurium allergic patients who were offered triple testing [31, 32], diagnosis was confirmed by ST and at least one *in vitro* test in 6 (60%).

Table E4 in this article's Online Repository, summarizes the results from our cross-reactivity studies by ST. The pair with the highest prevalence of cross-reactivity is atracurium and cisatracurium. Suxamethonium and cisatracurium reactors rarely demonstrated cross-reactivity.

Latex

79 patients (18.0%) were latex allergic; 47 (59.5%) of them presented life-threatening reactions. In 56.1% reactions occurred after 30 minutes after exposure. MCA was demonstrable in 15/19 (78.9%). In 60/79 patients, diagnosis rested upon congruent sIgE and SPT results. In the rest, diagnosis was mainly confirmed by unequivocal sIgE tests or a combination of sIgE and molecular diagnostic investigations [33, 34] excluding irrelevant sensitisation to cross-reactive carbohydrate determinants and profilin [35].

Antibiotics

67 antibiotic allergies were identified, accounting for 15.3% of allergic POH reactions (figure 1). Life-threatening anaphylaxis was present in 50 patients. Fifty-five were caused by cefazolin. MCA was present in 29/33 cases, 26 of these 29 presented life-threatening reactions. All reactions to antibiotics occurred within 30 minutes after administration, in 3 events symptoms started before induction. Diagnosis of cefazolin allergy mainly rested upon skin testing [36].

Chlorhexidine

Chlorhexidine allergy was documented in 45 patients (10.3%). In 33 (73.3%) patients there was a life-threatening reaction generally occurring within 30 minutes after exposure. Nine patients had their intervention abandoned. In 25/45 patients (55.6%) diagnosis of chlorhexidine allergy rested upon a concordant positive sIgE and ST result. The remainder had their diagnosis confirmed by sIgE with exclusion of alternative causes or a combination of sIgE and BAT [37].

Patent and methylene blue

Ten episodes (2.3%) related to a dye (patent blue N.=7, methylene blue N.=3) mainly applied for sentinel mapping. Seven reactions were life-threatening. Onset varied from minutes to 1.5h after administration. None of the patients with cancer surgery needed rescheduling. Allergy to dyes was documented by ST sometimes complemented with BAT [38].

Miscellaneous

In 6 patients a diagnosis of gelatine allergy was made (life-threatening, N.=4). All patients had a positive ST, but only 2 demonstrated a positive sIgE. Despite ubiquitous use of opioids, we observed only one case of fentanyl allergy. Other rare causes were ethylene oxide, heparin, mannitol (paracetamol), methyl-prednisolone-sodium-succinate, ondansetron, sugammadex amongst others.

Unidentified (unexplained) events

As summarized in figure 1, amongst the 608 cases in the dataset, no explanation was found in 196 cases (32.1%). 107 (54.9%) out of them suffered non-life-threatening reactions, 89 had life-threatening reactions. However, a grade 4 was rare (N.=15, 7.7%). From the 132 cases whom had their intervention stopped, 24 remained unexplained.

Follow-up after perioperative hypersensitivity

456 of the 608 patients who demonstrated a POH could be queried about subsequent anesthesia following our diagnostic investigations. 203 reported one or more new surgical interventions, and anesthetic/surgical notes were obtained in 156 cases. All had uneventful anesthesia, except one chlorhexidine allergic patient who was inadvertently re-exposed. From the 103 patients who were re-exposed to a NMBA, 27 were initially diagnosed as NMBA allergic (mainly rocuronium N.=22), 38 had an alternative cause identified, and in 38 no culprit was delineable. All 22 rocuronium allergic patients were uneventfully exposed to a benzylisoquinoline that tested negative (cisatracurium N.=15, atracurium N.=5 and mivacurium N.=3). Of the 76 cases in whom no NMBA allergy was established and who had an NMBA during subsequent anesthesia, 28 patients were re-exposed to the same NMBA that was administered at the time of the index reaction (rocuronium N.=20, cisatracurium N.=4 and

atracurium N.=4). It is of note that, 18 out of the 27 patients with a NMBA allergy who uneventfully had an alternative NMBA during subsequent anesthesia demonstrated a positive sIgE to morphine.

Discussion

Despite numerous efforts aiming at describing clinical manifestations and the epidemiology of POH, significant gaps remain in our knowledge. Limited studies investigated administration, timing/dosing of adrenaline and fluids, both critical to successful treatment of life-threatening anaphylaxis [39-42]. For example, Kemp *et al,* have identified gaps in preparedness and referral for further investigation [12] and NAP6 revealed that investigations of POA can have significant shortcomings [2, 10, 11].

Our study confirms POH to manifest with varying clinical severity with life-threatening anaphylaxis occurring in over two-thirds of adults and one-third of children. Admittedly, it is possible these ratios might deviate, mainly because of non-referral of milder cases but life-threatening reactions likely occur more frequently in adults because of underlying comorbidities and intake of antihypertensive drugs [41, 43]. Considering the clinical manifestations, cardiovascular symptoms such as hypotension, arrhythmia and ischemia were almost universal, paralleling observations by others [1, 2, 14, 18, 39, 40, 44]. Bronchospasms and mucocutaneous symptoms were noticed less frequently thereby potentially hindering and/or delaying recognition. Time-of-onset was less than 30 minutes in three-quarters of cases across all severity grades. Although we cannot exclude delayed recognition of non-life-threatening reactions, life-threatening reactions appeared to start earlier. Paralleling observations by others, neither time-of-onset nor clinical presentation explained the reaction [8, 14, 45, 46].

Our data confirm that the management of POH can significantly deviate from the treatment recommendations [47-49]. Like others [2, 39-42], we observed that adrenaline and fluids were not always administered as recommended, despite impressive rapid progression of the reaction. Intravenous adrenaline was administered in approximately three-quarters of life-threatening reactions. Fluids were administered in less than half of the patients. The explanation(s) for this non-adherence to recommendations are multiple but certainly extend beyond difficulties in recognizing anaphylaxis during anesthesia and surgery. To some extent, reluctance could also stem from excessive caution with adrenaline among anaesthetists, or failure to understand that early adrenaline can help stabilise mast cells and mitigate the reaction. . Hopefully studies like those by Currie *et al* [39], Garvey *et al* [40] and Reiter *et al* [41], together with the findings and recommendations of NAP6 [42] will improve and standardize management of perioperative anaphylaxis. Perhaps such studies could analyze the importance of

duration and extend of hypotension to determine the optimal approach of anaesthetized patients with a systolic BP < 50 mmHg [2, 13, 50] and the reason why some cases resist adrenaline [41] and might need additional treatments such as methylene blue [51] and extracorporeal membrane oxygenation (ECMO) [52].

Paralleling observations by others [2, 53], it appears that patients can have their surgery completed once hemodynamically stabilized, even when they required CPR. However, as life-threatening anaphylaxis entails a risk for complications [2, 19, 53], the decision to continue surgery needs an individual risk-benefit assessment between emergency and indication.

Although the result of acute serum tryptase does not necessarily reflect MCA nor does it predict the culprit, demonstration of MCA provides valuable information about the mechanism involvement in a POH reaction and adds rigor to the diagnosis. Therefore, it is recommended to sample acute tryptase in every suspicion of a POH [49, 54-60]. Moreover, a consensus equation for interpretation of acute tryptase [29] has been validated in POH [61]. In line with others [9, 14, 15, 40, 62-64], we found that obtaining acute tryptase measurements and reporting of timing of sampling remains challenging. This highlights the need for increased awareness of tryptase measurements amongst anesthetists to improve rates of sampling [54, 58]. Nevertheless, we made some relevant findings. Quantification of acute tryptase was most frequently available in life-threatening reactions and adults MCA was significantly more observed in life-threatening reactions. In line with others [43, 65, 66], acute tryptase levels were found to be significantly higher in severe reactions but in 10% of MCA-cases, the acute value remained below the classical decision threshold of 11.4 µg/L. Finally, like others [8, 9, 14, 43, 63, 65, 66] we failed to identify an acute or baseline tryptase level or acute/baseline tryptase ratio that proved absolutely discriminating between immune and non-immune reactions. Collectively, these findings indicate that we should abandon arbitrarily chosen thresholds and that sampling of acute tryptase should not be restricted to severe cases [67].

The predominant cause of POH are NMBA, mainly rocuronium. From NMBA reactors, a majority presented rapid onset life-threatening anaphylaxis with MCA. Results of ST and *in vitro* tests suggest NMBA-related reactions generally to result from an IgE-dependent process rather than from off-target occupation of the MRGPRX2 receptor [3-5, 68]. Because sIgE-inhibition studies and ST have shown cross-reactivity between NMBA to attain 60-80%[1, 8, 9, 14, 15, 17, 69-74], diagnosis of NMBA allergy requires cross-reactivity studies with identification of safe alternatives for subsequent anaesthesia [13, 49, 56, 57, 75]. Our study confirms that cross-reactivity between all NMBA is unusual [1, 8, 69, 73, 74], but is most prevalent between benzylisoquinolines and that single agent sensitization is most frequently seen in patients reacting to suxamethonium [8, 73]. Furthermore, cross-reactivity is not necessarily bidirectional [1]. For

example, 84.6% of atracurium reactors demonstrate cross-reactivity to cisatracurium. *Vice versa*, "only" 28.6% of cisatracurium reactors exhibit cross-reactivity to atracurium. The exact reason(s) cross-reactivity not to be bidirectional remain(s) elusive. Probably it relates to the fact sensitization to NMBA, which is mainly seen in drug naïve patients, to result from sensitization to (an) unknown compound(s) generating heterogeneous responses with distinct IgE reactivity profiles exhibiting different affinity. Alternatively, it cannot be firmly be excluded discrepancies in cross-reactivity to result from uncertainties associated with the optimal concentrations of IDT [1, 14, 76, 77]. *Mutatis mutandis*, these explanations apply to the interclass cross-reactivity, *e.g.* between rocuronium and suxamethonium, and rocuronium and cisatracurium. We confirm that BAT might benefit cross-reactivity studies, especially in patients yielding negative or equivocal ST responses [72, 78]. Finally, unlike some French authors [8, 18] who use their own marker for testing responses to NMBA harbouring quaternary substituted ammonium structures [79, 80], we dissuade the use of sIgE morphine in isolation to diagnose NMBA allergy or predict cross-reactivity [26, 30, 32]. Alternatively, we confirm that *in vitro* testing for NMBA can remain positive for many years [1]. Consequently, we do not adhere to the proposal not to perform these tests later than 3 years after the reaction [81]. It should be kept in mind that sIgE morphine is unreliable in detecting sensitization to benzylisoquinolines [32, 82, 83].

The 2nd most commonest cause for POH is latex, but compared to the our prior study [15], its significance seems decreasing probably because of the introduction of alternative elastomers. Largely half of the cases presented with life-threatening reactions and in many cases, time-of-onset exceeded 30 minutes. Latex allergy was generally documented by ST and sIgE, as an isolated positive latex-sIgE result can be misleading mainly because of interference by clinically irrelevant anti-profilin and anti-cross-reactive carbohydrate antibodies. Such irrelevant sensitizations are demonstrable in up to a quarter of patients with pollen and hymenoptera venom allergy [35]. In such patients BAT [84] and molecular diagnostic testing [34] might benefit correct diagnosis of *Hevea* latex allergy.

Antibiotics, mainly cefazolin and amoxicillin/clavulanic acid, constitute the 3rd cause of POH in our study. However, as compared to earlier findings, it is likely antibiotics to shift to the second position [15]. Most of antibiotic allergic patients presented with life-threatening reactions and had their diagnosis diagnosed by ST [36, 85]. The NAP6 study [86] showed that the choice of antibiotic prophylaxis is influenced by preoperative penicillin allergy history in a quarter of the patients who received teicoplanin or vancomycin, and, thereby probably contributing to the high incidence of teicoplanin-induced anaphylaxis [2]. With the knowledge that history of penicillin allergy is spurious in over 90% of cases, effective de-labelling is mandatory to optimize antibiotic stewardship [87-90]. Like others [91-93], we observed cefazolin allergy is generally selective [36]. *Vice versa*, it appears that cefazolin is generally safe in patients with a history of penicillin allergy, especially when history is vague [94-96].

In our series, chlorhexidine accounted for 10% of all cases. In a majority of the patients, time-of-onset was rapid and reactions were severe, frequently requiring discontinuation of surgery [2, 10, 14, 52, 63, 97, 98]. As the assessment of chlorhexidine exposure during the perioperative setting is not always straightforward, chlorhexidine should systematically be tested in case of a POH reaction, even in countries with limited usage [9].

Since the mid-1960s, blue dyes have been recognized to be a rare cause of POH, with patent blue mostly being employed in Europe and isosulfan blue, the highly cross-reactive isomer of patent blue, widely used in the USA. Methylene blue has no structural similarity, but cross-reactivity has been described [99]. Most cases of dye-related reactions were life-threatening and time-of-onset varied from minutes to 1.5h after administration like in other series [2, 45, 46]. It is likely this delay to mirror slow absorption from subcutaneous tissue and lymphatics and/or delay of recognition because of interference with pulse oximetry with (prolonged) artificial lowering of readings [100]. As in other series [2, 45, 46, 99], allergy to dyes was mainly documented by ST. BAT was rarely needed [38].

In 6 patients, a diagnosis of gelatine allergy was made. SIgE rarely benefited diagnosis, irrespective the cause of the gelatine allergy [101].

In about one-third of patients, no culprit was delineable. Although many authors assume these patients suffered from a sIgE-independent reaction [8, 9, 14, 18], we prefer to describe these reactions to originate from unknown mechanism(s). It cannot be excluded that the failure to identify a cause to merely result from incorrect referral or insufficient test-sensitivity rather than to reflect an alternative (non-immune) mechanism. Anyway, as the absence of a diagnosis can pose a significant risk [102, 103], further efforts seem mandatory to improve tests performances and to unravel alterative mechanisms. As cutaneous MC bear the MRGPRX2 receptor, we do not presume that this receptor is involved in POH with negative investigations [6]. Moreover, as cutaneous MC - unlike basophils [104] - express MRGPRX2, a positive ST does not necessarily reflect an immune, i.e. IgE-mediated, reaction [4]. Alternatively, when ST and BAT yield congruent positive results, the evidence is strong for an IgE-mediated mechanism, as opposed to off-target occupation of MRGPRX2.

The best assurance of safe subsequent anesthesia is a documented safe anesthetic. Therefore, we conducted a follow-up study to analyze the effectiveness of our diagnostic approach, particularly of NMBA allergy. NMBA not only constitute the predominant cause of POH in our region [14, 15], but also do not lend themselves to full-dose DPT for obvious reasons. We managed to review over 150 anesthetic/surgical notes. Revisions largely confirmed several findings from the literature [17, 20-28]. Failure to prevent a POH during subsequent anesthesia was rare. However, we observed that anesthetists frequently substitute the NMBA in subsequent anesthesia. Only 28 patients had the same

NMBA that tested negative in ST and BAT. Alternatively, we observed negative ST rocuronium might not always give the green light for safe re-exposure, and that BAT might benefit diagnosis in difficult cases with negative or equivocal ST results [68]. However, an isolated positive sIgE for morphine should not preclude further use of NMBA. Finally, sadly, compliance with the requests to notify information regarding subsequent anesthesia was extremely poor, and probably reflects the failure of anesthetists to appreciate the importance of updating the patients' records with details of uneventful subsequent anesthesia. *Verba volant, scripta manent!*

As with any study of this nature, there are limitations to this study. Part of our findings might relate to a referral bias with an underrepresentation of non-life-threatening reactions. The main reasons for non-referral of such cases probably include non-recognition of milder cases and lack of knowledge regarding need for diagnostic tests in milder reactions. We firmly encourage anesthetists not to restrict their referral for diagnostic investigation to anaphylaxis and/or patients demonstrating MCA but also to refer milder grades even in the absence of MCA. Due to the life-threatening character of anaphylaxis, anesthetists are mainly engaged in stabilizing the patient rather than registering events and filling in notes. The registration is done *a posteriori*, making items such as timing, doses, volumes, duration sometimes incomplete and less reliable for correct reporting. Due to the retrospective design, data are missing. However, in view of the size of our study and our efforts to capture data, we are confident that our findings add to our knowledge about POH. During longitudinal studies, not seldom and unavoidable, some practices might change. In this study, we were "confronted" with the venue of new tests, lowering of sIgE decision-thresholds, altered ST concentrations (rocuronium, cefazolin).

In conclusion, POH constitutes a serious condition with significant consequences of non-recognition and misdiagnosis. This study highlights that there is room for both an improved acute management and diagnostic work-up. Moreover, the introduction of novel diagnostic tools should not only benefit diagnosis but might also shift paradigms in mechanisms and identification of therapeutic targets.

Contributorship Statement:

Ebo D.G.: study set-up, patient inclusion, discussing results and analyses, writing of the manuscript, correcting and proof reading of the manuscript.

Van Gasse A.L.: patient inclusion, data analyses, writing of the manuscript, correcting and proof reading of the manuscript.

Decuyper I.I.: patient inclusion, data analyses, correcting and proof reading of the manuscript.

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Hagendorens M.M.: correcting and proof reading of the manuscript.

De Clerck L. S.: correcting and proof reading of the manuscript.

Sabato V.: study set-up, patient inclusion, discussing results and analyses, writing of the manuscript, correcting and proof reading of the manuscript.

Acknowledgements

DGE is a Senior Clinical Researcher of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1800614N). ALVG is a fellow of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1113617N). VS is a Senior Clinical Researcher of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1804518N).

Legends of figures

Figure 1: Composition of the study population. The perioperative hypersensitivity data set comprises 608 patients (40 children, 568 adults). 208 cases demonstrated non-life-threatening reactions, 400 life-threatening reactions. A culprit was identified in 412 cases (67.8%). In 27 (6.5%) cases a second offender was identified, giving a total of 439 culprit agents in 412 cases. MCA: mast cell activation, NMBA: neuromuscular blocking agents. MCA was defined as peak tryptase exceeding 1.2x(baseline tryptase) + 2 µg/L.

Figure 2: Clinical presentation of life-threatening and non-life-threatening reactions.

Figure 3: Treatment of life-threatening and non-life-threatening reactions. IV: intravenous.

Figure 4: Baseline and acute serum tryptase levels (N.=250). The line denotes the median. The decision threshold recommended by the manufacturer is 11.4 µg/L.

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