

Acute Management, Diagnosis, and Follow-Up of Suspected Perioperative Hypersensitivity Reactions in Flanders 2001-2018



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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 75.7% and 31%, respectively. 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 workup that should certainly not be restricted to patients with severe reactions and/or showing mast cell activation.

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. A total of 456 patients demonstrating a POH could be queried about subsequent anesthesia.

RESULTS: A total of 608 cases formed the final dataset; 208 had a non-life-threatening reaction and 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 75.7% and 31%, respectively, 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 were neuromuscular blocking agents, latex, cefazolin, and dyes. A total of 156 cases had uneventful anesthesia, except 1 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 workup that should not be restricted to patients with severe reactions and/or showing MCA. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2194-204)

Key words: Epidemiology; Allergy; Perioperative hypersensitivity; Management; Diagnosis

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/workup, 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 (eg, bronchospasms during difficult intubation). Mucocutaneous

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Abbreviations used

<i>BAT</i>	<i>Basophil activation test</i>
<i>BP</i>	<i>Blood pressure</i>
<i>CPR</i>	<i>Cardiopulmonary resuscitation</i>
<i>DPT</i>	<i>Drug provocation test</i>
<i>IDT</i>	<i>Intradermal test</i>
<i>IV</i>	<i>Intravenous</i>
<i>MC</i>	<i>Mast cell</i>
<i>MCA</i>	<i>Mast cell activation</i>
<i>MRGPRX</i>	<i>Mas-related G protein coupled receptor X</i>
<i>NAP6</i>	<i>Sixth National Audit Project</i>
<i>NMBA</i>	<i>Neuromuscular blocking agent</i>
<i>POH</i>	<i>Perioperative hypersensitivity</i>
<i>SE</i>	<i>Standard error</i>
<i>sIgE</i>	<i>Specific IgE</i>
<i>SPT</i>	<i>Skin prick test</i>
<i>ST</i>	<i>Skin test</i>

signs of POH can also be invisible due to the surgical drapes covering the patient or due to 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 nonimmune reactions are administered simultaneously. For example, since the first description by McNeil et al,³ neuromuscular blocking agents (NMBA) have increasingly been suggested to trigger mast cell (MC) degranulation by off-target occupation of the mas-related G protein coupled receptor X2 (MRGPRX2) receptor. Moreover, some authors have proposed to reclassify NMBA hypersensitivity as nonimmune reactions.⁴⁻⁶ Finally, causes of POH might show geographical differences⁷ and changes over time,^{8,9} hampering generalization and comparison of epidemiologic 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 the absence of a harmonized diagnostic approach.^{2,10-12} To improve the 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 at www.jaci-inpractice.org. 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 to the NAP6 scale.¹³

Allergic workup included total IgE, specific IgE (sIgE), baseline tryptase, skin prick tests (SPT), intradermal tests (IDT), basophil activation tests (BAT), and drug provocation tests (DPT). [Table E1](#) (available in this article's Online Repository at www.jaci-inpractice.org) shows the nonreactive skin test concentrations, and [Table E2](#) (available in this article's Online Repository at www.jaci-inpractice.org) displays the diagnostic procedures for the most important causes of POH. Mast cell activation (MCA) was defined as peak tryptase exceeding $1.2 \times (\text{baseline tryptase}) + 2 \mu\text{g/L}$.²⁹ In the presence of MCA, positive confirmatory testing was considered as proof of an immune-mediated reaction. In contrast, patients with MCA but negative diagnostic workup were considered to have presented a nonimmune reaction.

A total of 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. A total of 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 (eg, anxiety, difficult intubation, subcutaneous emphysema, and over dosage). The remainder presented only mild isolated symptoms such as erythema, bronchospasms, and lowered tension without biological evidence of 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 were present in 96.7% (381/394) and 48.7% (169/347), respectively. 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 , $P < .001$). In 5 cases, life-threatening anaphylaxis preceded induction.

As indicated in [Figure E1](#) (available in this article's Online Repository at www.jaci-inpractice.org), clinical presentation was more severe in adults (68%) than in children (35%) (χ^2 , $P < .001$). Only 1 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 blood pressure (BP) < 50 mm Hg had no cardiopulmonary resuscitation (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

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

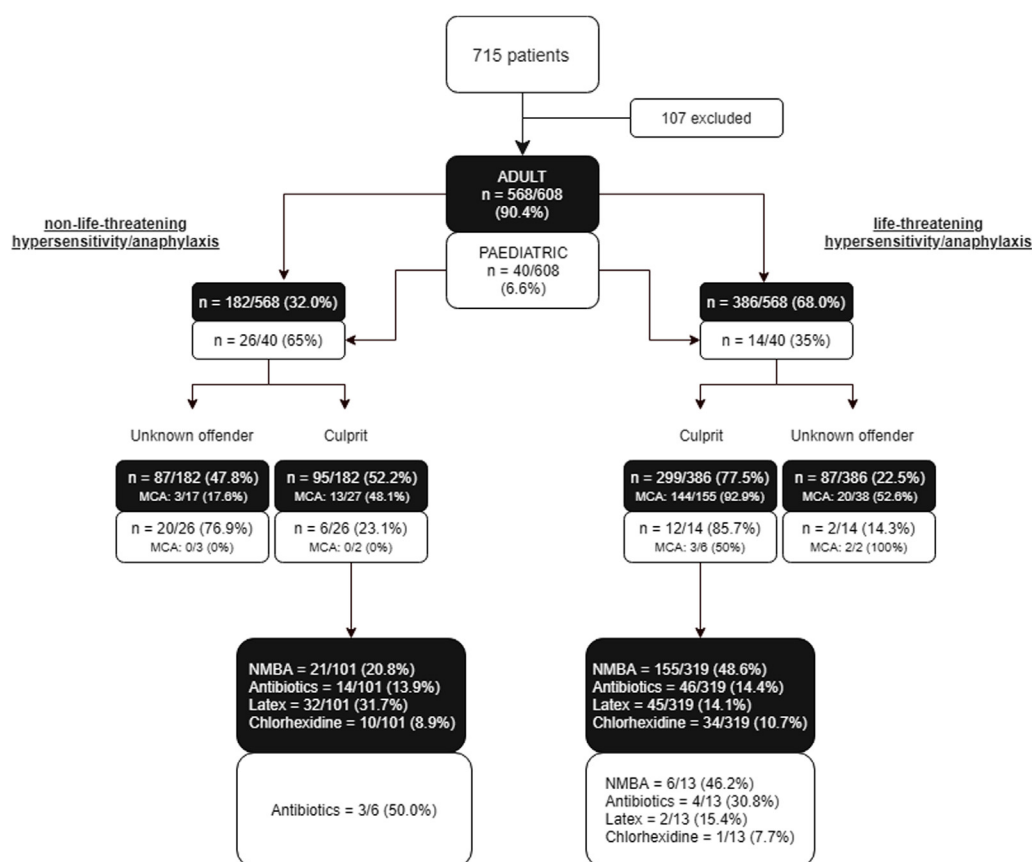


FIGURE 1. Composition of the study population. The perioperative hypersensitivity data set comprises 608 patients (40 children, 568 adults). A total of 208 cases demonstrated non-life-threatening reactions, and 400 life-threatening reactions. A culprit was identified in 412 cases (67.8%). In 27 cases (6.5%), a second offender was identified, giving a total of 439 culprit agents in 412 cases. MCA was defined as peak tryptase exceeding $1.2 \times (\text{baseline tryptase}) + 2 \mu\text{g/L}$. MCA, Mast cell activation; NMBA, neuromuscular blocking agents.

non-life-threatening reactions (204/400 vs 50/208, χ^2 , $P < .001$). MCA could be calculated in 250 cases (237 of 568 adults [41.7%] and 13 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 , $P < .001$). Importantly, 19 (10.3%) of the patients demonstrating MCA had an acute tryptase $<11.4 \mu\text{g/L}$. MCA was more frequent in adults than in children (180/237 [75.9%] vs 5/13 [38.5%], χ^2 , $P = .014$).

As illustrated in Figure 4, mean (standard error, SE) of acute tryptase in life-threatening reactions (41.5 $\mu\text{g/L}$, SE = 3.64) was higher than in non-life-threatening reactions (9.6 $\mu\text{g/L}$, SE = 1.26) (t -test, $P < .001$). Baseline tryptase levels did not differ between life-threatening (5.7 $\mu\text{g/L}$, SE = 0.24) and non-life-threatening reactions (5.1 $\mu\text{g/L}$, SE = 0.23).

Figures E2 and E3 in this article's Online Repository at www.jaci-inpractice.org show results about MCA, acute and baseline tryptase, and delta tryptase (acute-baseline) in relation to the underlying mechanistic process, that is immune versus nonimmune. In immune responses, MCA is more frequent (160/185 vs 30/65, χ^2 , $P < .001$). However, neither 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 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 of 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 versus 101 cases (48.6%) in the non-life-threatening group (χ^2 , $P < .001$). Predominant culprits in adults and children were NMBA, latex, and antibiotics (Figure E4, available in this article's Online Repository at www.jaci-inpractice.org). Table E3 in this article's Online Repository at www.jaci-inpractice.org 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).

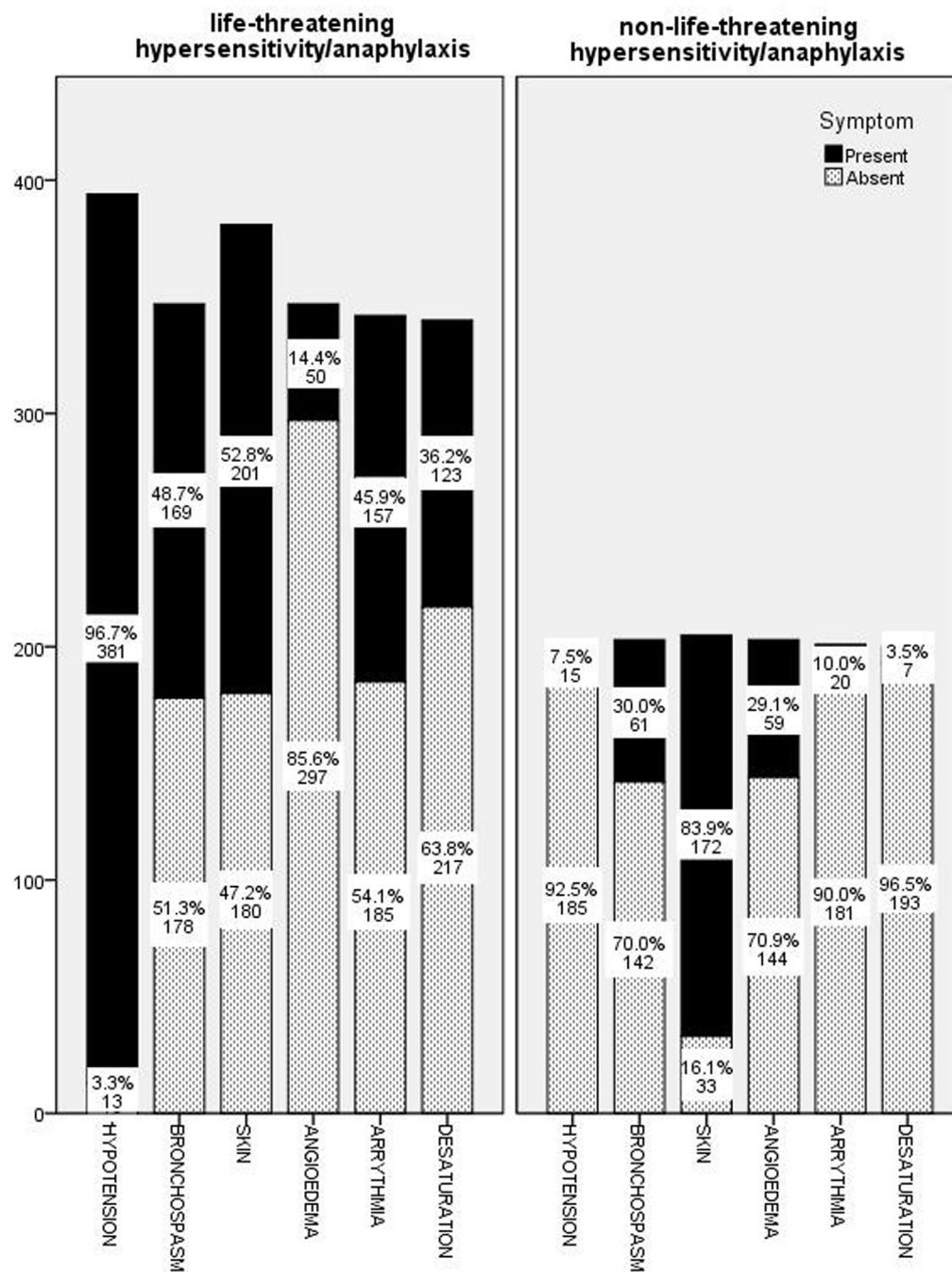


FIGURE 2. Clinical presentation of life-threatening and non-life-threatening reactions.

Neuromuscular blocking agents. 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 E5 in this article's Online Repository at www.jaci-inpractice.org displays the distribution of sensitization to the NMBA.

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

In 123 patients with rocuronium allergy who had triple diagnostic tests,³⁰ diagnosis was confirmed by skin tests (STs) and at least 1 *in vitro* test in 93 (75.6%). Nine patients with negative STs had their diagnosis documented by combination of BAT and sIgE, or BAT. In 11 patients with suxamethonium allergy, ST and at least 1 *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 1 *in vitro* test in 6 (60%).

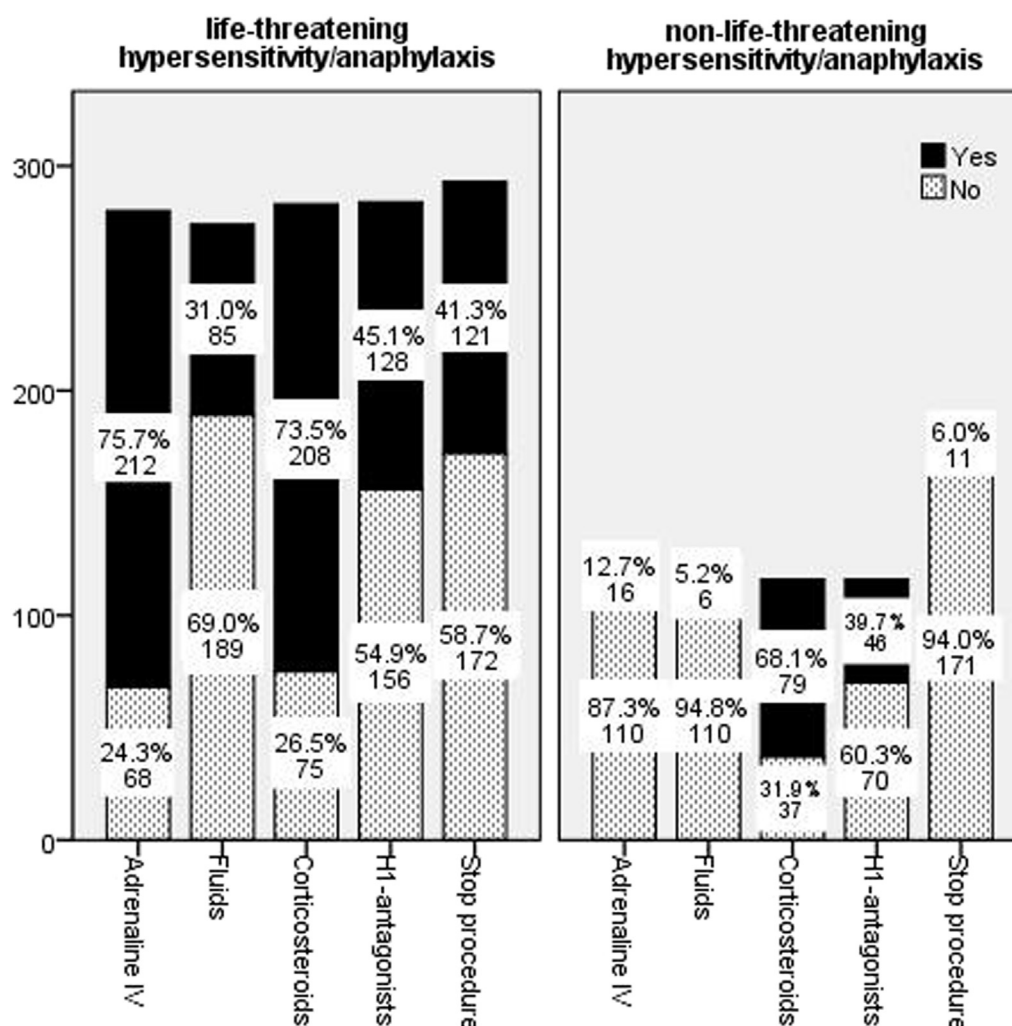


FIGURE 3. Treatment of life-threatening and non-life-threatening reactions. IV, Intravenous.

Table E4 in this article's Online Repository at www.jaci-inpractice.org 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. A total of 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 of 19 (78.9%). In 60 of 79 patients, diagnosis rested on 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. A total of 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 of 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 on skin testing.³⁶

Chlorhexidine. Chlorhexidine allergy was documented in 45 patients (10.3%). In 33 patients (73.3%), there was a life-threatening reaction generally occurring within 30 minutes after exposure. Nine patients had their intervention abandoned. In 25 of 45 patients (55.6%), diagnosis of chlorhexidine allergy rested on 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 1.5 hours 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

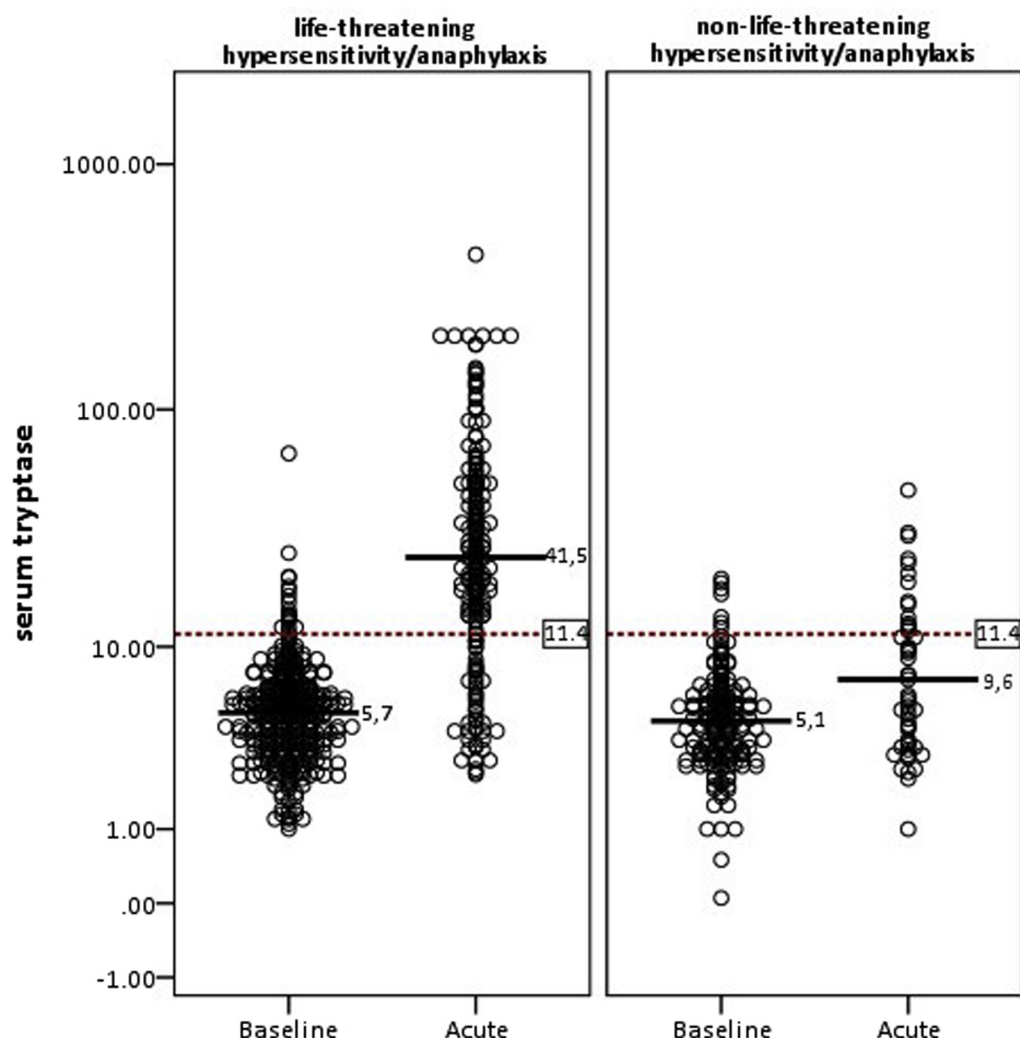


FIGURE 4. Baseline and acute serum tryptase levels (N = 250). The line denotes the median. The decision threshold recommended by the manufacturer is 11.4 µg/L.

use of opioids, we observed only 1 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%). Of these, 107 (54.9%) suffered non-life-threatening reactions, and 89 had life-threatening reactions. However, a grade 4 was rare (N = 15, 7.7%). From the 132 cases who had their intervention stopped, 24 remained unexplained.

Follow-up after POH

Of the 608 patients who demonstrated a POH, 456 could be queried about subsequent anesthesia after our diagnostic investigations. A total of 203 reported 1 or more new surgical interventions, and anesthetic/surgical notes were obtained in 156 cases. All had uneventful anesthesia, except 1 chlorhexidine allergic patient who was inadvertently re-exposed. From the 103

patients who were re-exposed to an 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 (cis-atracurium 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 of the 27 patients with an 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 and timing/dosing of adrenaline and fluids, both critical to

successful treatment of life-threatening anaphylaxis.³⁹⁻⁴² For example, Kemp et al¹² have identified gaps in preparedness and referral for further investigation, 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 more than two-thirds of adults and one-third of children. Admittedly, it is possible that 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. IV 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 nonadherence 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 anesthesiologists, or failure to understand that early adrenaline can help stabilize MCs and mitigate the reaction. Hopefully, studies like those by Currie et al,³⁹ Garvey et al,⁴⁰ and Reitter 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 extent of hypotension to determine the optimal approach of anesthetized patients with a systolic BP < 50 mm Hg^{2,13,50} and the reason why some cases resist adrenaline⁴¹ and might need additional treatments such as methylene blue⁵¹ and extracorporeal membrane oxygenation.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 tryptase²⁹ 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 anesthesiologists 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 nonimmune 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 is NMBA, mainly rocuronium. From NMBA reactors, a majority presented rapid onset life-threatening anaphylaxis with MCA. Results of ST and *in vitro* tests suggest that NMBA-related reactions generally 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% to 80%,^{1,8,9,14,15,17,69-74} diagnosis of NMBA allergy requires cross-reactivity studies with identification of safe alternatives for subsequent anesthesia.^{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 benzyloquinolines, 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) of cross-reactivity not to be bidirectional remain(s) elusive. Probably it relates to the fact that sensitization to NMBA, which is mainly seen in drug-naïve patients, results from sensitization to (an) unknown compound(s) generating heterogeneous responses with distinct IgE reactivity profiles exhibiting different affinity. Alternatively, it cannot be firmly excluded that discrepancies in cross-reactivity result from uncertainties associated with the optimal concentrations of IDT.^{1,14,76,77} *Mutatis mutandis*, these explanations apply to the interclass cross-reactivity, for example, 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 harboring 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 benzyloquinolines.^{32,82,83}

The second most commonest cause for POH is latex, but compared with 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 antiprolin 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, BAT⁸⁴ and molecular diagnostic testing³⁴ might benefit correct diagnosis of Hevea latex allergy.

Antibiotics, mainly cefazolin and amoxicillin/clavulanic acid, constitute the third cause of POH in our study. However, as compared with earlier findings, it is likely that antibiotics shift to the second position.¹⁵ Most of antibiotic-allergic patients presented with life-threatening reactions and had their diagnosis confirmed by ST.^{36,85} The NAP6 study⁸⁶ 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 the history of penicillin allergy is spurious in over 90% of cases, effective delabeling is mandatory to optimize antibiotic stewardship.⁸⁷⁻⁹⁰ Like others,⁹¹⁻⁹³ we observed that 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 United States. 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 1.5 hours after administration like in other series.^{2,45,46} It is likely that this delay mirrors 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 of the cause of the gelatine allergy.¹⁰¹

In approximately one-third of patients, no culprit was delineable. Although many authors assume that 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 merely results from incorrect referral or insufficient test sensitivity rather than to reflect an alternative (nonimmune) mechanism. Anyway, as the absence of a diagnosis can pose a significant risk,^{102,103} further efforts seem mandatory to improve test performances and to unravel alternative mechanisms. As cutaneous MCs bear the MRGPRX2 receptor, we do not presume that this receptor is involved in POH with negative investigations.⁶ Moreover, as cutaneous MCs—unlike basophils¹⁰⁴—express MRGPRX2, a positive ST does not necessarily reflect an immune, that is, 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 more than 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 anesthesiologists frequently substitute the NMBA in subsequent anesthesia. Only 28 patients had the same NMBA that tested negative in ST and BAT. Alternatively, we observed that 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 anesthesiologists 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 nonreferral of such cases probably include nonrecognition of milder cases and lack of knowledge regarding need for diagnostic tests in milder reactions. We firmly encourage anesthesiologists 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. Because of the life-threatening character of anaphylaxis, anesthesiologists 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, and duration sometimes incomplete and less reliable for correct reporting. Because of 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, and altered ST concentrations (rocuronium, cefazolin).

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

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ONLINE REPOSITORY

METHODS

This study involves 715 referrals to our outpatients' clinic because of a suspected perioperative hypersensitivity (POH) reaction, between January 1, 2001, and May 31, 2018. Collected data included details of demographics, history of allergy, previous anesthesia, drugs administered, exposition to other potential culprits (eg, latex, antiseptics, and dyes), clinical presentation, management and timings related to the event, quantifications of tryptase, and details of diagnostic investigations. POH reactions were classified corresponding to the Sixth National Audit Project grading scale.^{E1} As some causes might exhibit slower onset,^{E2} and according to the current consensus classification of immediate drug hypersensitivity,^{E3} time-of-onset for inclusion as a POH was maximally up to 2 hours after induction of general or locoregional anesthesia. Finally, we expanded our follow-up study on the predictive values of neuromuscular blocking agent (NMBA) tests,^{E4} by revision of the medical and anesthetic records of patients who had subsequent anesthesia.

The methods are described elsewhere,^{E5-E7} but summarized here for clarity.

Allergic workup included total IgE and specific IgE toward latex and components, chlorhexidine, ethylene oxide, suxamethonium, rocuronium, atracurium, morphine, gelatin, penicilloyl G, penicilloyl V, ampicilloyl, and amoxicilloyl using the ImmunoCAP FEIA technique (Phadia Thermo Fisher, Uppsala, Sweden). Decision thresholds were set according to the recommendations of the manufacturer, except for rocuronium (0.13 kUA/L) and suxamethonium (0.11 kUA/L), as these cutoffs were demonstrated to yield optimal combined sensitivity and specificity.^{E8}

Baseline tryptase was quantified by the ImmunoCAP FEIA technique (Phadia Thermo Fisher). Mast cell activation was defined when peak tryptase exceeded $1.2 \times (\text{baseline tryptase}) + 2 \mu\text{g/L}$.^{E9}

Skin prick tests (SPT) and intradermal tests (IDT) were performed according to the recommendations of the Société Française d'Anesthésie et de Réanimation^{E10} that were updated and published in the paper by Mertes et al.^{E6} For β -lactam antibiotics, see the paper by Brockow et al.^{E11} Briefly, SPT were

performed on the ventral part of the forearm and implied histamine 10 mg/mL (HAL Allergy Benelux BV, Leiden, the Netherlands) as a positive control to assess skin test reactivity, a saline buffer solution as a negative control to exclude cutaneous hyperreactivity (dermographism), administered drugs (and potential cross-reactive structures as well as alleged safe alternatives), and systematically latex and chlorhexidine. SPT were read after 15 minutes and considered positive when the wheal of the wheal and flare reaction exceeded 3 mm. If needed, patients with negative SPT had additional (serial dilutions) IDT. IDT responses were considered positive when the wheal of the wheal and flare reaction equaled or exceeded 5 mm or when the wheal had doubled as compared with the injection bleb of 0.02 mL. Maximal concentrations used for SPT and IDT are summarized in Table E1.

Basophil activation tests were performed as described elsewhere.^{E7} Briefly, the test—that relies on flow cytometric analysis of *in vitro* activated basophils—includes identification of the cells as a primary step and subsequently analysis of their activation with a positive control (anti-IgE), a negative control (stimulation buffer without any drug), and stimulation with relevant drugs (mainly NMBA,^{E15,E16} latex,^{E17} chlorhexidine,^{E18} rifamycin,^{E19} dyes,^{E20} etc.). Results are expressed as net percentage of CD63⁺ basophils, that is, expression of CD63 after allergen stimulation minus spontaneous CD63 expression. Note that allergen-specific thresholds were adopted.

When indicated, a graded drug provocation test up to a cumulative dose equaling or exceeding the therapeutic dose was performed, except for NMBA and chlorhexidine.

Table E2 displays the diagnostic procedures organized for the most important causes of POH. No tests were performed that were deemed unnecessary.

A total of 456 patients demonstrating a POH could be queried about subsequent anesthesia. Additional anesthetic/surgical notes were obtained in 156 cases who had anesthesia after diagnostic workup.

Statistical analyses

Statistical analysis implied independent sample *t*-test and χ^2 analyses where appropriate (SPSS Statistics 24, IBM, Chicago, Ill). $P \leq .05$ was considered significant.

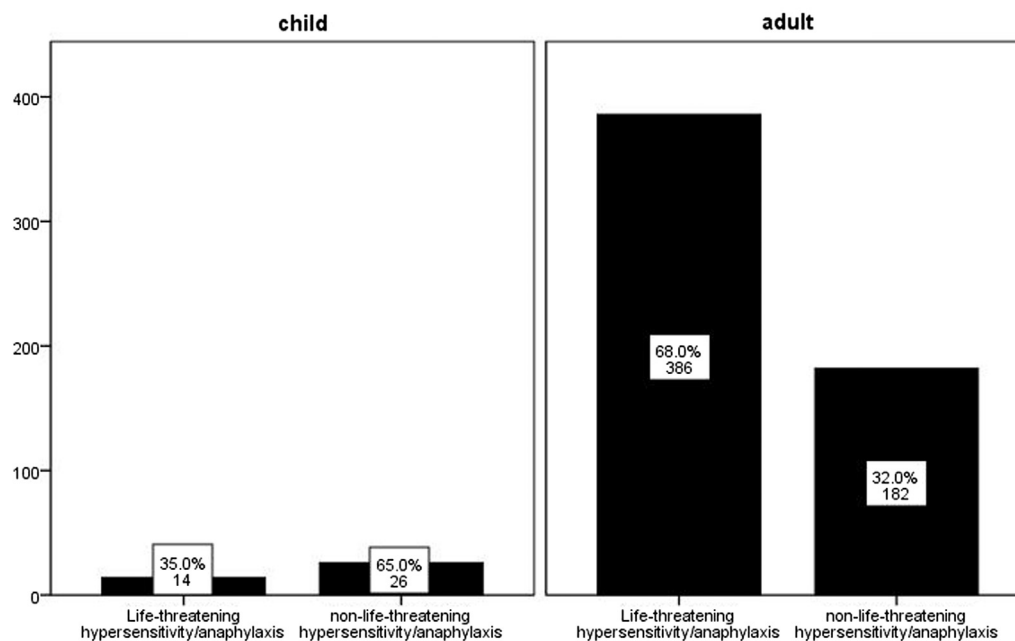


FIGURE E1. Numbers and percentages of life-threatening and non-life-threatening reactions in children and adults. This figure shows a comparison between 40 children and 568 adults. Clinical presentation was more severe in adults (68%) than children (35%) (χ^2 , $P < .001$). Only 1 child demonstrated a grade 4.

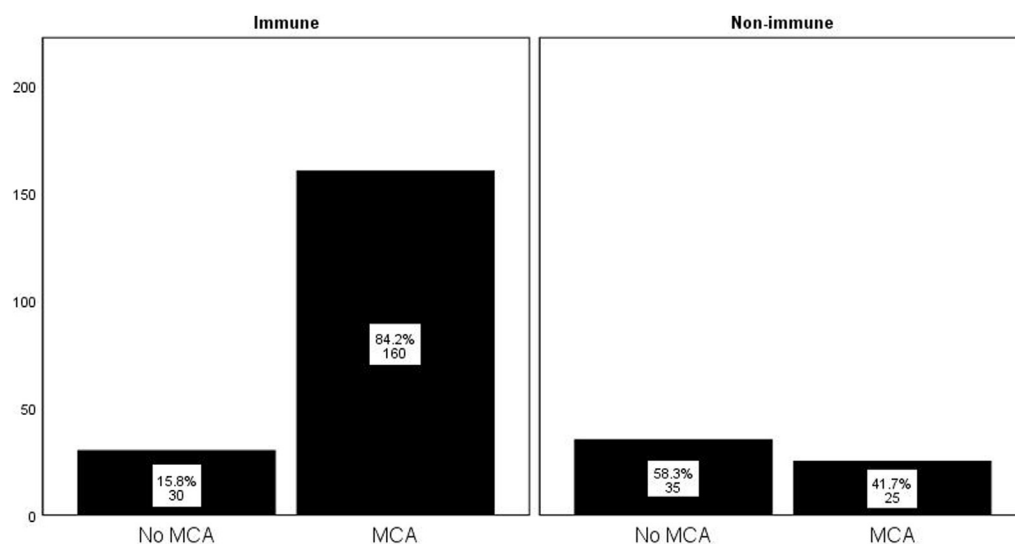


FIGURE E2. Numbers and percentages of the presence and absence of mast cell activation (MCA) in relation to the underlying mechanistic process.

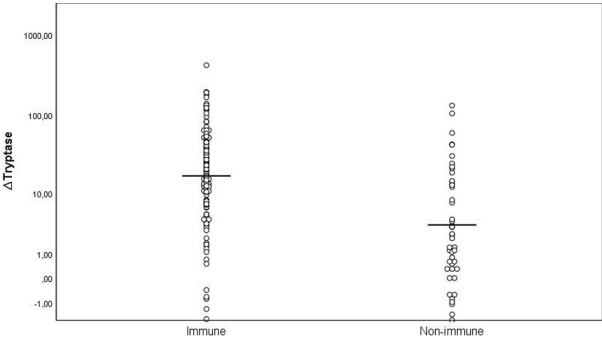


FIGURE E3. Difference in tryptase (acute minus baseline) in relation to the underlying mechanistic process.

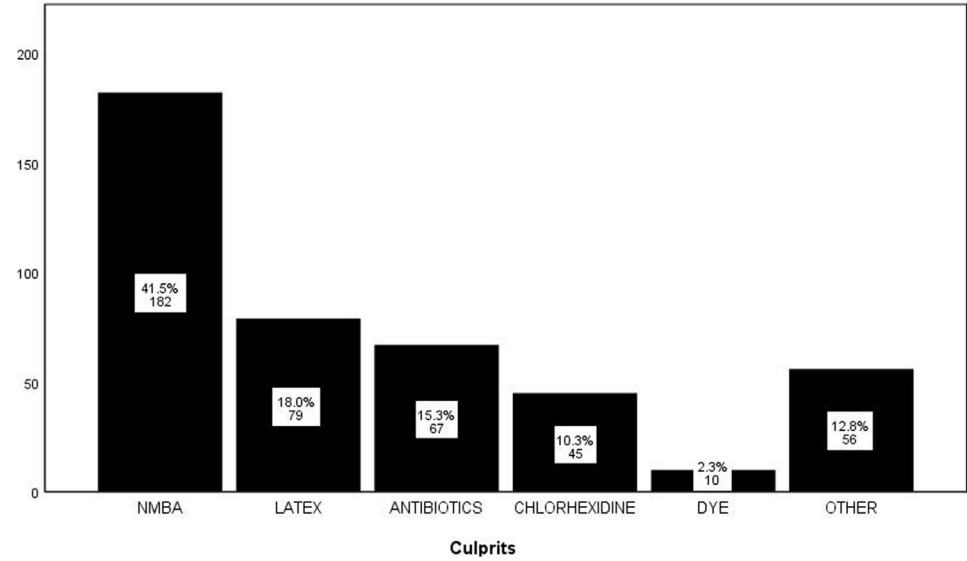


FIGURE E4. Numbers and percentages of main culprits. *NMBA*, Neuromuscular blocking agents.

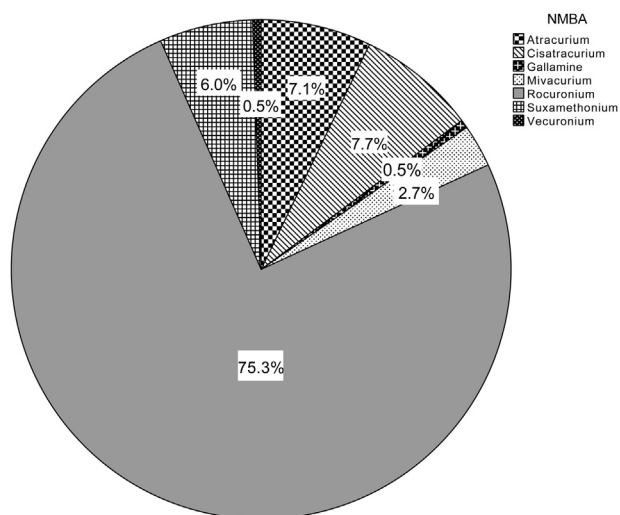


FIGURE E5. Distribution of sensitization to neuromuscular blocking agents (NMBA). From the 182 NMBA-related reactions, 137 were attributable to rocuronium, 14 to cisatracurium, and 13 to atracurium. According to the usage of NMBA, reactions occurred in 11 of 17 (64.7%) for suxamethonium, 137 of 333 (41.1%) for rocuronium, 5 of 17 (29.4%) for mivacurium, 14 of 58 (24.1%) for cisatracurium, and 13 of 79 (16.6%) for atracurium.

TABLE E1. Nonreactive skin test concentrations (mostly encountered products)

Agent	Skin prick test		Intradermal test (IDT)		µg/mL
	mg/mL	Dilution	mg/mL	Dilution	
Atracurium	10	1/10	1	1/1000	10
Cisatracurium	2	Undiluted	2	1/100	20
Mivacurium	2	1/10	0.2	1/1000	2
Pancuronium	2	Undiluted	2	1/10	200
Rocuronium*	10	Undiluted	10	1/200	50
Suxamethonium	50	1/5	10	1/500	100
Vecuronium	4	Undiluted	4	1/10	400
Etomidate	2	Undiluted	2	1/10	200
Midazolam	5	Undiluted	5	1/10	500
Propofol	10	Undiluted	10	1/10	1000
Thiopental	25	Undiluted	25	1/10	2500
Ketamine	10	1/10	10	1/10	1000
Alfentanil	0.5	Undiluted	0.5	1/10	50
Fentanyl	0.05	Undiluted	0.05	1/10	5
Remifentanyl	0.05	Undiluted	0.05	1/10	5
Sufentanil	0.005	Undiluted	0.005	1/10	0.5
Chlorhexidine	0.5	Undiluted	0.5	1/100	5
Povidone iodine	100	Undiluted	100	1/10	10000
Patent blue	25	Undiluted	25	1/10	2500
Methylene blue	10	Undiluted	10	1/100	100
Benzylpenicillin [†]	10.000 IU		10.000 IU		
Amoxicillin/ampicillin	20		20		
Cephalosporins [‡]	2		2		
Heparins		Undiluted		1/10	
Local anesthetics		Undiluted		1/10	
Patent blue		Undiluted		1/10	
Methylene blue		Undiluted		1/100	

IU, International unit.

Note that we did not rely on skin testing to document morphine hypersensitivity, as skin tests have proven to be unreliable to diagnose opiate hypersensitivity.^{E14}

*During the study period, the recommendation for maximal concentration tests for IDT with rocuronium was changed from a 1/100 dilution (0.01 mg/mL) to 1/200 (0.05 mg/mL) dilution.^{E12}

[†]For benzylpenicillin skin test concentrations are expressed as IU, not mg/mL.

[‡]For cefazolin, since 2013, the maximal skin test concentration was 20 mg/mL, as this concentration was shown to be nonirritating and more sensitive than the recommended concentration of 2 mg/mL. This validation was published in the journal.^{E13}

TABLE E2. Diagnostic procedures organized for the most important causes of POH

	NMBA	Antibiotics (mainly β -lactam)	Latex	Chlorhexidine	Gelatine
Skin tests*	Standard	Standard	Standard	Standard	Standard
sIgE [†]	Standard	Standard	Standard	Standard	Standard
BAT [‡]	Standard	If required	Rarely	If required	If required
CRD	NA	NA	If required	NA	NA

NA, Not applicable; NMBA, neuromuscular blocking agent; POH, perioperative hypersensitivity; sIgE, specific IgE.

*For drugs skin testing starts with skin prick tests (SPT), additional intradermal tests are restricted to patients with negative or equivocal SPT.

[†]All sIgE measurements are performed using the ImmunoCAP FEIA method (Phadia Thermo Fisher).

[‡]Basophil activation tests (BAT) are performed when skin testing and/or sIgE yield negative or equivocal results. Since the venue of component resolved diagnosis (CRD), BAT is rarely needed for documenting latex allergy.

TABLE E3. Major culprits— changes over time

	January 2001-May 2018 (N = 608) Culprit identified in 412 (67.8%)	January 2001-December 2011 (N = 344) Culprit identified in 246 (71.5%)
<i>Agent</i>		
NMBA	41.5%	40%
Hevea latex	18.0%	25%
Antibiotics	15.3%	12%
Chlorhexidine	10.3%	9%
Double sensitizations	6.5%	7%

NMBA, Neuromuscular blocking agents.

TABLE E4. Cross-reactivity between NMBA measured by skin testing

	Rocuronium	Cisatracurium	Atracurium	Suxamethonium
Rocuronium		18/134 (13.4%)*	8/130 (6.2%)	38/132 (28.8%) ^{†,‡}
Cisatracurium	1/14 (7.1%)		4/14 (28.6%) [§]	0/14
Atracurium	0/13	11/13 (84.6%) [§]		0/13
Suxamethonium	0/11 [‡]	2/11 (18.2%)	2/11 (18.2%)	

BAT, Basophil activation test; NMBA, neuromuscular blocking agents; sIgE, specific IgE.

*All 18 patients had a negative BAT for cisatracurium, and in 10 patients, skin test responsiveness for cisatracurium was restricted to the intradermal test at the highest concentration.

[†]Of these 38, 26 patients (68.4%) also demonstrated a positive BAT and/or sIgE to suxamethonium.

^{‡,§}Pairs with the highest prevalence of cross-reactivity. Cisatracurium—atracurium (χ^2 , $P = .003$), rocuronium—suxamethonium (χ^2 , $P = .038$).

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