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Perioperative Hypersensitivity Reactions: Culprit Agents and Management Outcomes

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ABSTRACT

Objective: To identify culprit agents in patients evaluated for suspected perioperative hypersensitivity and to assess the safety of subsequent anesthetic procedures guided by allergological evaluation.

Materials and Methods: This retrospective observational study included 34 patients referred with suspected perioperative hypersensitivity. All patients underwent a standardized allergological work-up including skin prick tests, intradermal tests, and drug provocation tests when appropriate. Reaction severity was classified according to the Ring and Messmer scale. Patients were categorized as having a confirmed culprit or idiopathic reactions.

Results: Of the 34 patients, 23 were female (67.6%), and the mean age was 50.8 ± 14.9 years. Reactions most frequently occurred during the emergence phase (14/34, 41.2%), followed by the induction phase (13/34, 38.2%). Patients reacting during the emergence phase were significantly older (median 61 years) than those reacting during induction or maintenance (p=0.001). A culprit agent was identified in 13 patients (38.2%), and a total of 15 culprit agents were identified in this group; antiseptics were the most frequent (6/15, 40.0%), particularly chlorhexidine (5/15, 33.3%). A history of atopy was more frequent in the confirmed group (4/13, 30.8% vs. 0/21, 0%; p=0.015). All patients underwent subsequent surgery under an evaluation-guided anesthesia plan, and no immediate hypersensitivity reactions occurred at first re-exposure.

Conclusion: Antiseptics, especially chlorhexidine, were the most frequently identified cause of perioperative hypersensitivity in this cohort. Advanced age and delayed reaction onset may help guide suspicion toward cutaneous sensitizers. A standardized allergological evaluation is essential for ensuring safe future anesthetic exposure.

Keywords: Perioperative hypersensitivity, anaphylaxis, chlorhexidine, antiseptics, drug allergy

INTRODUCTION

Perioperative hypersensitivity (POH) ranges from mild symptoms to life-threatening anaphylaxis, with a reported mortality rate of 3–10% (1). While incidence estimates vary due to methodological differences, large-scale audits, such as the Sixth National Audit Project (NAP6), consistently place severe reactions at approximately 1:10,000 anesthetics (2-4). Diagnosis is exceptionally challenging, as simultaneous administration of multiple potent drugs and the patient's unconscious state—often obscured by surgical drapes—mask clinical signs (1,2,5). Furthermore, differentiating POH from non-allergic complications, such as hypotension due to hemorrhage or bronchospasm from airway instrumentation, remains difficult (2,5). These confounding factors often contribute to delayed recognition and suboptimal management, highlighting an urgent need for standardized diagnostic and therapeutic strategies (4,5).

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The etiology of POH demonstrates marked geographical variability, yet neuromuscular blocking agents (NMBAs) and antibiotics consistently remain the most frequent triggers globally. While NMBAs continue to represent the predominant cause in countries such as France, Belgium, and Norway, recent large-scale audits, including the NAP6 in the United Kingdom, alongside data from Spain and the United States, indicate that antibiotics have surpassed NMBAs as the leading culprit (2,4,6). Within these epidemiological shifts, the incidence of natural rubber latex allergy has significantly declined, largely due to the widespread implementation of avoidance strategies and latex-free environments (2). Conversely, Sugammadex, increasingly used to reverse rocuronium-induced neuromuscular blockade, has been identified as an emerging, though rare, cause of anaphylaxis (2,7). Given the complexity of these exposure patterns and the potential for severe outcomes, the accurate identification of the offending agent and the determination of safe alternatives are essential to prevent life-threatening recurrence in future anesthetic procedures.

Despite the availability of international guidelines, real-world data regarding the specific etiology and management outcomes of POH in our region remain limited. Furthermore, while identifying the culprit agent is critical, there is a paucity of data evaluating the safety of subsequent anesthetic procedures following allergological work-up. Therefore, the primary aim of this study was to determine the culprit agents in patients referred to our tertiary center with suspected perioperative hypersensitivity. Secondarily, we aimed to evaluate the diagnostic value of in vivo and in vitro tests and, crucially, to assess the success of management strategies in ensuring safe re-exposure during future surgeries.

MATERIALS and METHODS

Study Design

This retrospective observational study was conducted at a tertiary referral allergy center and included patients referred for evaluation of suspected perioperative hypersensitivity reactions between January 2020 and December 2025.

Study Population and Data Collection

Data regarding patient demographics (age, gender), medical history (atopy, known drug or food allergies, number of previous surgeries), and detailed characteristics of the index reaction were retrospectively retrieved from the hospital's electronic medical records and allergy clinic archives. Comorbid conditions, including asthma, hypertension, diabetes mellitus, and cardiovascular disease, were also recorded based on documented medical history. For each case, the timing of the reaction, specific clinical manifestations, and acute management steps were systematically recorded. For the purpose of standardized classification, anesthesia phases were operationally defined as follows: the induction phase was defined as the period from the initiation of anesthetic drug administration until airway securing and/or the start of the planned procedure; the maintenance phase encompassed the interval during which anesthesia was maintained for the procedure; and the emergence/recovery phase was defined as the period from the cessation of anesthetic agents until extubation and early postoperative recovery in the operating room. Additionally, for patients with a history of perioperative hypersensitivity who were scheduled for re-operation, preoperative screening data were systematically collected to evaluate management outcomes. This included the results of in vivo testing performed with alternative agents, specifically skin prick tests (SPT), intradermal tests (IDT), and, where feasible, drug provocation tests (DPT).

A total of 37 patients were referred with a preliminary diagnosis of perioperative hypersensitivity. Two patients were excluded because their clinical history was not consistent with perioperative hypersensitivity reactions, and one patient was excluded because the index event was determined to represent a drug adverse effect rather than a hypersensitivity reaction. The remaining 34 patients constituted the final study population and underwent a complete allergological evaluation.

The clinical severity of POH in all study participants was classified using the standard four-grade severity scale defined by Ring and Messmer (8). According to this classification, reactions were categorized as follows: Grade I, presenting with cutaneous signs only (e.g., generalized erythema, urticaria, angioedema); Grade II, characterized by moderate multisystem involvement including hypotension, tachycardia, or bronchospasm (cough, difficulty in ventilation) in addition to mucocutaneous signs; Grade III, defined as a life-threatening reaction with severe hypotension/shock, marked bronchospasm, and loss of consciousness; and Grade IV, consisting of cardiac and/or respiratory arrest.

Allergological Work-up

Allergological investigations were performed at least 4 weeks after the initial reaction to avoid false-negative results due to the refractory period, in accordance with the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) and the European Network for Drug Allergy (ENDA) (9,10). The standard test panel included all pharmacological agents (neuromuscular blocking agents, opioids, antibiotics, local anesthetics, etc.) and substances (latex, chlorhexidine, povidone-iodine) to which the patient had been exposed during the perioperative period.

In Vivo Tests

In vivo skin testing was performed in accordance with the recommendations of the EAACI and the ENDA.

Allergological testing included both agents administered during the index perioperative reaction and alternative agents considered for subsequent surgical procedures, based on clinical input from the anesthesia team.

SPTs were performed as the first-line diagnostic approach using commercially available test solutions of suspected drugs and antiseptics, including chlorhexidine and povidone-iodine. Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively, and a wheal diameter of ≥3 mm greater than the negative control after 20 minutes was considered positive. In patients with negative SPT results and persistent clinical suspicion, IDTs were subsequently performed using serial dilutions prepared according to EAACI/ENDA recommendations, starting from low concentrations and increasing stepwise to the maximal non-irritating concentration for each agent. An increase in wheal diameter of ≥3 mm compared to the initial bleb, accompanied by erythema, was considered a positive result. The concentrations and dilutions used for both SPTs and IDTs are detailed in Supplementary Table II. Skin test results were interpreted in conjunction with the clinical history and the temporal relationship to the index perioperative reaction.

Drug Provocation Tests

DPT was considered the gold standard for confirming the safety of alternative drugs (e.g., local anesthetics, antibiotics, analgesics) or excluding hypersensitivity when skin tests were inconclusive (11). DPTs were performed only when clinically indicated and considered safe, in a hospital setting with full resuscitation facilities available, using a graded challenge protocol (placebo-controlled, single-blinded) until the therapeutic dose was reached.

Diagnostic Classification

For analysis, a "confirmed" diagnosis was defined as the identification of a perioperative agent with a positive in vivo test result and a plausible temporal relationship to the index reaction; reactions without an identifiable agent after complete evaluation were classified as "idiopathic".

Ethics Approval

This study was approved by the local ethics committee (Approval No: 2025/6197). Written informed consent was not required for this retrospective review in accordance with local regulations.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (minimum-maximum) depending on the distribution of the data. Categorical variables were presented as frequencies (n) and percentages (%). The normality of distribution for continuous variables was assessed using the Shapiro-Wilk test. For the comparison of two independent groups (Confirmed vs. Idiopathic), Student's t-test was used for normally distributed data. In contrast, the Mann-Whitney U test was used for non-normally distributed data. To compare three groups based on reaction timing (Induction, Maintenance, Emergence), the Kruskal-Wallis test was employed. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate (when expected cell counts were <5). A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 34 patients with a history of POH were included in the study. The demographic and clinical characteristics of the patients are summarized in Table I. The study population was predominantly female (23/34, 67.6%), with a mean age of 50.8 ± 14.9 years. A history of drug allergy was reported in 29.4% (10/34) of patients, while 11.8% (4/34) had a history of atopy.

Table I: Demographic and Clinical Characteristics of the Study Population (n=34)

Parameter	Value
Age (years), mean ± SD	50.8 ± 14.9
Gender, n (%)	
Female	23 (67.6)
Male	11 (32.4)
Medical History, n (%)	
Atopy	4 (11.8)
Drug Allergy History	10 (29.4)
Food Allergy History	1 (2.9)
Comorbidities, n (%)	
Asthma	6 (17.6)
Hypertension	6 (17.6)
Diabetes mellitus	5 (14.7)
Cardiovascular disease	2 (5.9)
Timing of Reaction, n (%)	
Induction	13 (38.2)
Maintenance	7 (20.6)
Emergence/Recovery	14 (41.2)
Severity (Ring & Messmer), n (%)	
Grade I (Cutaneous only)	18 (52.9)
Grade II (Moderate)	6 (17.6)
Grade III (Life-threatening)	6 (17.6)
Grade IV (Cardiac/Resp. Arrest)	4 (11.8)
Epinephrine Administration	10 (29.4)
Diagnostic Outcome, n (%)	
Idiopathic (Unknown)	21 (61.8)
Confirmed (Culprit Identified)	13 (38.2)
Antiseptics: Chlorhexidine (n=5), Povidone-iodine (n=1) Hypnotics / Sedatives: Ketamine (n=2), Midazolam (n=1) Antibiotics: Ornidazole (n=1), Rifampicin (n=1) Opioids: Remifentanil (n=1), Tramadol (n=1) Neuromuscular blocking agents: Rocuronium (n=1) Latex: (n=1)	

*The total number of identified culprit agents (n=15) exceeds the number of patients with confirmed hypersensitivity (n=13) due to polysensitization in two patients.

Regarding the timing of the hypersensitivity reactions, the highest frequency was observed during the emergence/recovery phase (14/34, 41.2%), followed by the induction phase (13/34, 38.2%). Reactions during the maintenance phase were less frequent (7/34, 20.6%). Clinically, more than half of the patients (18/34, 52.9%) presented with Grade I reactions characterized by isolated mucocutaneous signs, while severe reactions (Grade III and IV) accounted for 29.4% (10/34) of cases. Epinephrine was administered to 29.4% (10/34) of patients during acute management.

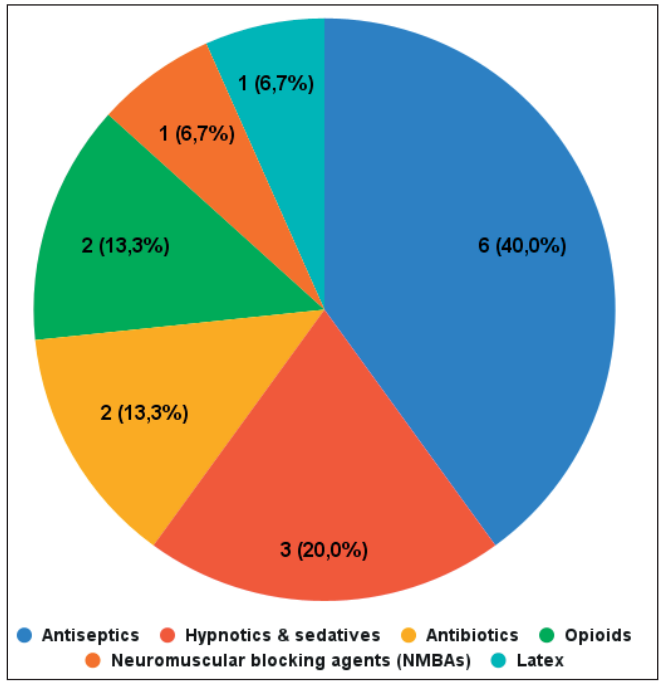

Figure 1: Frequency distribution of identified culprit agents. The total number of identified agents (n=15) exceeds the number of patients with confirmed hypersensitivity (n=13) because of polysensitization in two patients (one with NMBA and Latex, one with Antibiotic and Antiseptic).

Following a comprehensive allergological work-up, a culprit agent was identified in 13 (38.2%) patients (Confirmed Group), whereas the etiology remained unidentified in 21 (61.8%) patients (Idiopathic Group). As shown in Figure 1, antiseptics were the leading identified trigger (6/15, 40.0%), comprising chlorhexidine (5/15, 33.3%), followed by povidone-iodine (1/15, 6.7%). Hypnotics and sedatives accounted for three identified agents, including ketamine (2/15, 13.3%) and midazolam (1/15, 6.7%). Other identified culprits included opioids (remifentanil and tramadol) (2/15, 13.3%), antibiotics (ornidazole and rifampicin) (2/15, 13.3%), neuromuscular blocking agents (rocuronium) (1/15, 6.7%), and latex (1/15, 6.7%). Polysensitization was detected in two cases.

The comparison between the confirmed and idiopathic groups revealed a statistically significant difference regard-

Table II: Comparison of demographic and clinical characteristics according to diagnostic outcome

Parameter	Confirmed Group (n=13)	Idiopathic Group (n=21)	p-value
Age (years), mean ± SD	55.4 ± 16.2	48.0 ± 13.6	0.235
Gender (Female), n (%)	9 (69.2)	14 (66.7)	1.000
Medical History, n (%)			
Atopy	**4 (30.8)**	**0 (0.0)**	**0.015***
Drug Allergy History	4 (30.8)	6 (28.6)	1.000
Reaction Timing, n (%)			0.951
Induction	5 (38.5)	8 (38.1)	
Maintenance	3 (23.1)	4 (19.0)	
Emergence	5 (38.5)	9 (42.9)	
Severity (Ring & Messmer), n (%)			1.000
Grade I (Cutaneous only)	6 (46.2)	12 (57.1)	
Grade II-IV (Mod-Severe)	7 (53.8)	9 (42.9)	
Epinephrine Use, n (%)	4 (30.8)	6 (28.6)	1.000

Table III: Analysis of clinical parameters according to the timing of reaction onset

Parameter	Induction (n=13)	Maintenance (n=7)	Emergence (n=14)	p-value*
Age (years), Median (Min-Max)	**42 (29-67)**	**36 (27-56)**	**61 (40-80)**	**0.001**
Gender (Female), n (%)	9 (69.2)	5 (71.4)	9 (64.3)	0.936
Confirmed diagnosis, n (%)	5 (38.5)	3 (42.9)	5 (35.7)	0.951
Severity, n (%)				0.079
Grade I (Mild)	9 (69.2)	1 (14.3)	10 (71.4)	
Grade II-IV (Mod-Severe)	4 (30.8)	6 (85.7)	4 (28.6)	

*p-values from the Kruskal–Wallis test for continuous variables and chi-square or Fisher's exact test for categorical variables.

ing atopy. A history of atopy was present in 30.8% (4/13) of the confirmed group but was absent in the idiopathic group (0/21, 0%; p=0.015). No significant differences were observed between the two groups in age, gender, reaction time, or severity (Table II).

Further analysis of clinical parameters by reaction-onset timing revealed a significant difference in patient age. Patients reacting during the emergence phase were significantly older (Median: 61 years) compared to those reacting during induction (Median: 42 years) or maintenance (Median: 36 years) (p=0.001). Although reactions during the maintenance phase tended to be more severe (6/7, 85.7% Grade II-IV), the difference was not statistically significant (p=0.079) (Table III).

After allergological evaluation, all 34 patients underwent a subsequent surgical procedure under an anesthesia plan guided by the work-up. The identified culprit agents were avoided and replaced with tested-negative alternatives. In patients without an identified culprit and with negative testing, anesthesia was performed using tested-negative agents with standard precautions. No immediate hypersensitivity reactions occurred during the first subsequent procedure (0/34, 0%).

DISCUSSION

The present study evaluated the etiology and management outcomes of POH in a tertiary referral center. We observed three findings that differ from classical POH patterns (1): a predominance of antiseptics as the leading identifiable cause (2); a significant association between atopy and test-confirmed hypersensitivity (3); and a significant association between older age and reactions occurring during the emergence phase. In our cohort, subsequent anesthesia was guided by the allergological evaluation: identified culprit agents were avoided and replaced

by tested-negative alternatives, whereas in patients without an identified culprit, anesthesia was performed using agents with negative testing. No immediate hypersensitivity reactions occurred at the first re-exposure.

The identification of the causative agent in perioperative hypersensitivity is challenging because multiple drugs are administered simultaneously, and "hidden" exposures such as antiseptics may be undocumented (12-14). Previous studies have therefore reported that a culprit can be identified in only about 30–40% of cases (15,16). In our cohort, a culprit agent was identified in 38.2% of patients (13/34), which is consistent with these reports and provides context for the proportion of idiopathic reactions observed. This limited diagnostic yield reflects the constraints of current diagnostic methods, including the limited sensitivity and standardization of skin tests and the limited feasibility of drug-provocation testing for anesthetic agents (2,5,15,17). In addition, a proportion of reactions classified as idiopathic may be attributable to mechanisms that are not captured by routine allergological testing. These include non–IgE-mediated pathways, direct mast cell activation by certain anesthetic agents, or perioperative non-allergic events that may clinically mimic hypersensitivity reactions. Such mechanisms have been increasingly recognized in perioperative settings and may further explain the persistently high proportion of idiopathic cases despite comprehensive evaluation (2,5,13,14).

The identification of antiseptics as the predominant cause among confirmed cases (46.2%, 6/13) in our cohort appears to differ from historical trends favoring NMBAs and antibiotics (4,18). Similarly, a recent study from our country also reported NMBAs and opioids as the primary triggers (19). The distinct profile in our study may reflect the increasing recognition of chlorhexidine as a pervasive yet 'hidden' allergen (4,12). Ubiquitous in catheters and lubricants but often undocumented, chlorhexidine is frequently underdiagnosed if not specifically sought (18,20). Large-scale audits, such as NAP6, and data from the Danish Anaesthesia Allergy Centre report chlorhexidine prevalence rates ranging from 9% to 9.6% in centers where routine testing is employed (4,17); conversely, regions with less systematic screening or lower usage, such as France, report rates as low as <1% (21). Although povidone-iodine anaphylaxis is comparatively rare (18), its identification in our series confirms the potential relevance of topical agents. This predominance of antiseptics may contribute to the high frequency of emergence-phase reactions (41.2%). Unlike immediate-acting IV drugs, slower mucocutaneous absorption causes delayed symptoms that coincide with the end of surgery (12). Accordingly, late-onset reactions should prompt consideration of antiseptics as potential culprits.

Another demographic aspect of our cohort was that although women constituted the majority of the overall study population, no significant sex difference was observed among patients with a test-confirmed culprit agent. In the literature, female gender is a well-established risk factor for NMBA anaphylaxis, often attributed to cross-sensitization from quaternary ammonium compounds found in cosmetics (3,22). Conversely, chlorhexidine hypersensitivity frequently shows a male predominance (4,12). In our study, the absence of a sex difference in the confirmed group may reflect the etiological profile of the cohort, in which NMBAs played a minor role, and antiseptics constituted a substantial proportion of identified triggers.

A significant association was observed between a history of atopy and a confirmed diagnosis ($p=0.015$). While current literature generally states that atopy is not a risk factor for anaphylaxis to NMBAs (3), our findings reflect a specific etiological profile dominated by antiseptics (46.2% of confirmed cases). Reactions to these agents, particularly chlorhexidine, are well described as IgE-mediated hypersensitivity reactions (17,23). Unlike NMBAs, sensitization to antiseptics typically occurs via environmental exposure through the skin or mucous membranes. Emerging evidence suggests that the impaired skin barrier, a hallmark of the atopic constitution, may facilitate sensitization to such ubiquitous chemical agents (24). However, it is important to emphasize that this observation is based on a very small number of atopic patients (n=4). Therefore, this association should be interpreted with considerable caution and regarded as a preliminary observation, requiring validation in larger, adequately powered cohorts.

Conversely, a history of drug allergy was not associated with a confirmed diagnosis in our cohort. This finding is clinically relevant and consistent with both guideline recommendations and epidemiological data indicating that a history of other drug or food allergies does not increase the risk of perioperative hypersensitivity (2,3,14). Accordingly, our results are consistent with recommendations that preoperative risk stratification focus on a history of a previous unexplained perioperative event, the primary

established risk factor (13), rather than a non-specific history of drug hypersensitivity.

The significant association between older age and reactions during the emergence phase (p=0.001) may be related to the exposure profile of this subgroup, in which antiseptics constituted a substantial proportion of identified culprits. Unlike IV agents that trigger immediate symptoms upon induction, antiseptics applied to mucocutaneous surfaces require a latent period to be absorbed and reach systemic anaphylactogenic thresholds. This physiological delay often results in symptoms appearing towards the end of surgery (12,17). Accordingly, late-onset reactions in elderly patients should prompt consideration of 'hidden' cutaneous allergens such as chlorhexidine.

Our study has several limitations related to its retrospective, single-center design. The small sample size (n=34) limits the generalizability of our findings and reduces the power to detect less frequent associations. The absence of detailed data on specific surgical procedures also restricted a more refined assessment of exposure risks. Serum tryptase measurements were available in only a limited number of patients and therefore could not be systematically evaluated. Accordingly, these findings should be interpreted with caution and considered hypothesis-generating, and they require confirmation in larger, preferably multicenter, prospective cohorts. Nevertheless, the study's strength lies in its standardized allergological work-up, which facilitated the identification of clinically relevant culprits that are often underrecognized in routine practice.

In conclusion, our data indicate that antiseptics were the predominant identifiable cause of perioperative hypersensitivity in our study cohort, differing from classical patterns that favor neuromuscular blocking agents. A personal history of atopy and delayed reactions during the emergence phase—particularly in older patients—were more commonly observed among those with cutaneous sensitizers. In contrast, a non-specific history of drug allergy was not informative. Consideration of these clinical features may therefore help guide the diagnostic evaluation. Ultimately, a comprehensive allergological investigation remains essential to identify safe alternatives for future surgeries.

Conflict of Interest

The authors declare no conflicts of interest related to this work.

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Author Contributions

Concept: **Ferhat Sagun, Fatih Colkesen,** Design: **Ferhat Sagun, Fatih Colkesen,** Data collection or processing: **Ferhat Sagun, Mehmet Emin Gerek, Emrah Harman, Secim Kolak, Sukran Aslan Savas, Ismail Yigitdol,** Analysis or Interpretation: **Ferhat Sagun, Fatih Colkesen, Sevket Arslan,** Literature search: **Ferhat Sagun, Fatih Colkesen,** Writing: **Ferhat Sagun,** Approval: **All authors.**

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Supplementary Table SI: Patient-level results of allergological testing

Patient	Age	Sex	Rocuronium	Povidone-iodine	Neostigmine	Atropine	Atracurium	Tramadol	Pethidine	Midazolam	Bupivacaine	Cefazolin	Fentanyl	Remifentanil	Morphine	Propofol	Ketamine	Lidocaine	Prilocaine	Chlorhexidine	Ceftriaxone	Rifampicin	Moxifloxacin	Levofloxacin	Ornidazole	Gentamicin	Clindamycin	Sugammadex	Latex	Enoxaparin	Pantoprazole	Paracetamol
P01	61	F	-	-	-	-	NA	-	-	+	NA	NA	-	NA	-	-	NA	NA	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P02	36	F	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P03	60	F	-	NA	NA	NA	NA	NA	NA	-	NA	-	-	-	NA	-	NA	NA	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P04	80	F	-	-	NA	NA	NA	-	NA	-	NA	NA	-	NA	NA	-	NA	-	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P05	41	M	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	+	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P06	48	F	-	-	NA	NA	NA	-	NA	-	NA	NA	-	NA	-	-	NA	-	NA	-	NA	NA	NA	NA	+	-	-	NA	-	NA	NA	NA
P07	65	F	-	-	-	-	NA	+	NA	-	NA	NA	-	NA	-	-	NA	NA	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P08	42	F	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	-	NA	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
P09	73	F	-	-	NA	NA	NA	-	NA	-	NA	NA	-	-	-	-	NA	NA	NA	+	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA
P10	58	F	NA	-	NA	NA	NA	-	NA	-	NA	NA	-	-	NA	-	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	-	-	NA	NA	NA
P11	51	F	-	-	NA	NA	NA	-	NA	-	NA	NA	-	-	-	-	NA	-	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P12	63	M	NA	-	NA	NA	NA	NA	NA	-	NA	NA	-	NA	NA	-	NA	-	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P13	70	F	NA	-	NA	NA	NA	-	NA	-	NA	NA	-	-	-	-	+	NA	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P14	61	M	-	-	NA	NA	NA	-	NA	-	NA	NA	-	-	-	-	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P15	56	F	-	-	NA	NA	NA	NA	NA	-	NA	NA	-	-	NA	-	NA	-	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P16	37	F	NA	NA	NA	NA	NA	-	NA	-	NA	NA	-	-	-	-	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P17	44	F	NA	-	NA	NA	NA	NA	NA	-	NA	NA	-	-	NA	-	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P18	74	F	NA	NA	NA	NA	NA	-	NA	NA	-	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	-	-	NA
P19	54	M	-	NA	NA	NA	NA	NA	NA	-	-	NA	-	-	NA	-	NA	-	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
P20	61	F	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	-	NA	NA	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P21	29	F	NA	NA	NA	NA	NA	-	NA	-	-	NA	-	NA	NA	-	NA	NA	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P22	42	F	-	NA	NA	NA	NA	-	NA	-	NA	NA	-	NA	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA	NA
P23	40	F	-	-	NA	NA	NA	NA	NA	-	NA	NA	-	NA	NA	-	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P24	72	M	NA	-	NA	NA	NA	-	NA	-	NA	NA	-	-	-	-	NA	-	NA	-	-	NA	NA	-	NA	NA	NA	NA	-	NA	NA	-
P25	33	M	NA	NA	NA	NA	NA	-	NA	-	NA	NA	-	-	-	-	+	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P26	29	M	NA	NA	NA	NA	NA	-	NA	-	NA	NA	-	-	-	-	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P27	52	M	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	-	NA	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P28	32	F	-	NA	NA	NA	NA	NA	NA	-	NA	NA	-	NA	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
P29	67	M	NA	NA	NA	NA	NA	-	NA	-	NA	NA	-	-	-	NA	NA	NA	-	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P30	54	F	-	NA	NA	NA	NA	-	NA	-	NA	NA	-	-	-	-	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P31	46	M	-	NA	NA	NA	NA	-	NA	-	NA	NA	-	NA	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P32	33	M	NA	-	NA	NA	NA	NA	NA	-	NA	NA	-	+	-	-	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P33	27	F	-	-	NA	NA	NA	NA	NA	-	NA	NA	-	-	NA	-	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	-	NA	NA	NA
P34	38	F	+	-	NA	NA	-	-	NA	-	NA	NA	-	-	-	-	NA	-	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA

* "+" indicates a positive test result; "–" indicates a negative test result; "NA" indicates that the test was not performed. Sex: F = female; M = male.

Supplementary Table SII: Skin prick test concentrations and maximal non-irritating concentrations for intradermal testing (IDT).

Agent	SPT mg/mL	SPT Dilution	IDT mg/mL	IDT Dilution
Chlorhexidine	2	Undiluted*	0.002	1/1000
Povidone-iodine	100	Undiluted	-	Not performed
Rocuronium	10	Undiluted	0.05	1/200
Atracurium	1	1/10	0.01	1/100
Sugammadex	100	Undiluted	0.1	1/1000
Neostigmine	0.5	Undiluted	0.05	1/10
Atropine	0.5	1/10	0.005	1/100
Fentanyl	0.05	Undiluted	0.005	1/10
Remifentanil	0.05	Undiluted	0.005	1/10
Morphine	1	Undiluted	0.01	1/100
Pethidine	50	Undiluted	0.5	1/100
Tramadol	50	Undiluted	0.5	1/100
Propofol	10	Undiluted	1	1/10
Ketamine	50	Undiluted	5	1/10
Midazolam	5	Undiluted	0.5	1/10
Lidocaine	20	Undiluted	2	1/10
Prilocaine	20	Undiluted	2	1/10
Bupivacaine	5	Undiluted	0.5	1/10
Cefazolin	200	Undiluted	2	1/100
Ceftriaxone	20	Undiluted	2	1/10
Moxifloxacin	1.6	Undiluted	0.0016	1/1000
Levofloxacin	5	Undiluted	0.005	1/1000
Rifampicin	10	Undiluted	0.001	1/10000
Ornidazole	5	Undiluted	0.5	1/10
Gentamicin	40	Undiluted	4	1/10
Clindamycin	150	Undiluted	15	1/10
Latex	Extract	Undiluted	-	Not performed
Enoxaparin	100	Undiluted	10	1/10
Pantoprazole	4	Undiluted	0.4	1/10
Paracetamol	10	Undiluted	1	1/10

* Chlorhexidine: Tested as 2 mg/mL aqueous solution or 0.5% in alcohol.