APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Perioperative immediate hypersensitivity incidence, clinical characteristics, and outcomes after allergological evaluation: A multi-disciplinary protocol from tertiary hospital, Thailand

Thanachit Krikeerati,[1,2] Chamard Wongsa,[1,2] Torpong Thongngarm,[1,2] Patcharapong Rujirawan,[3] Nutsakol Borrisut,[3] Pattrapun Wongsripuemtet,[4] Papapit Tuchinda,[2,5] Yuttana Srinoulprasert,[2,3] Chanika Subchookul,[5] Chalisa Veerapong,[6] Pattarapa Khunsakdeeyodom,[6] Mongkhon Sompornrattanaphan[1,2]*

Abstract

Background: Perioperative immediate hypersensitivity reaction (POH) is an immediate hypersensitivity reaction during an anesthesiologist monitored procedure. We report data of clinically-suspected POH (csPOH) patients undergoing an allergist-performed unified diagnostic workup algorithm for POH.

Objective: To describe the characteristics of patients with csPOH, POH events, and the POH outcomes of procedures after the unified diagnostic workup algorithm for POH.

Methods: A cohort study on adults with csPOH was conducted at Siriraj Hospital, Thailand, covering events from January 2018 to August 2022. Diagnostic workup for POH by the allergist included an initial assessment, followed by comprehensive allergological evaluation. Patients were then follow-up for POH outcomes during subsequent anesthesia procedures.

Results: Of 68 patients were csPOH, only 52 patients were diagnosed with POH by allergists. The incidence was 1:4,304 anesthetic procedures for POH, and 1:11,900 anesthetic procedures for at least grade III POH. Most patients had a grade III (51.2%) or II (46.4%) reaction. The leading identified causative agents were antibiotics (36.8%), antiseptics (21%), latex (13.1%), and morphine (13.1%). Cefazolin and chlorhexidine were the most common antibiotic and antiseptic, respectively. During a median follow-up time of 2.1 years, all 14 patients completing comprehensive allergological evaluation underwent subsequent anesthesia without recurrence of POH.

Conclusion: The incidence of POH at our hospital was comparable to the global incidence. Antibiotics were the most common causative agent. Complete records, collaboration among the multidisciplinary team, and comprehensive evaluation of POH allow for safe subsequent procedures.

Key words: allergy, anesthesia, anaphylaxis, chlorhexidine, drug allergy, investigation, latex, perioperative hypersensitivity

Citation:
Krikeerati, T., Wongsa, C., Thongngarm, T., Rujirawan, P., Borrisut, N., Wongsripuemtet, P., Tuchinda, P., Srinoulprasert, Y., Subchookul, C., Veerapong, C., Khunsakdeeyodom, P., Sompornrattanaphan, M. (2025). Perioperative immediate hypersensitivity incidence, clinical characteristics, and outcomes after allergological evaluation: A multi-disciplinary protocol from tertiary hospital, Thailand. *Asian Pac J Allergy Immunol*, 43(3), 539-549. https://doi.org/10.12932/ap-150922-1456

Affiliations:
[1] Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[2] Faculty of Medicine Siriraj Hospital, Center of Research Excellence in Allergy and Immunology, Mahidol University, Bangkok, Thailand
[3] Department of Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[4] Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Affiliations (Continued):
[5] Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[6] Adverse Drug Reaction Unit, Pharmacy Department, Siriraj Hospital, Mahidol University, Thailand

*This author is an essentially intellectual contributor of this work

Corresponding author:
Mongkhon Sompornrattanaphan
Division of Allergy and Clinical Immunology, Department of Medicine
Faculty of Medicine Siriraj Hospital, Mahidol University
2 Prannok Road, Bangkoknoi Bangkok 10700, Thailand
E-mail: mongkhon.som@mahidol.ac.th

Introduction

Perioperative immediate hypersensitivity (POH) is an immediate hypersensitivity reaction during a procedure requiring anesthesia or an anesthesiologist monitoring, and the term POH covers all possible underlying mechanisms.[1,2] Perioperative anaphylaxis is the term used for a life-threatening reaction.[3]

POH is challenging for anesthesiologists and allergists because of numerous differential diagnoses, unusual clinical manifestations, and concurrently administered medications.[1] Avoiding causative drugs is an effective management for general drug allergies. However, this concept is not practical in the setting of POH. Avoiding all possible drugs without comprehensive allergological evaluation (CAE) may limit the choices of medications for future procedures, causing an unsafe and inappropriate depth of anesthesia. Furthermore, POH has detrimental physical, financial, and psychological disease effects, including near-fatal or fatal perioperative anaphylaxis leading to increased length of hospital stay and costs[4] and a high prevalence of post-traumatic stress disorder or other forms of psychological distress after anaphylaxis. Overall, reported mortality rates have been less than 5%.[4-6] CAE was reported to improve the outcome of subsequent anesthesia.[7] Thus, all patients with suspected POH should be referred for CAE, and planning for subsequent anesthesia should involve multidisciplinary team collaboration.

The estimated prevalence of perioperative allergic reactions in Thailand was 3.6%.[8] The possible causative agents associated POH were reported.[9] Antibiotics and neuromuscular blocking agents (NMBA) were the leading causes. However, there have been no reports from Thailand that used CAE to confirm the causative agents. Therefore, we aimed to describe the prevalence of POH, its causative agents, and the POH outcomes of subsequent anesthesia after CAE.

Methods

Study designs and subjects

A cohort study on adults with a csPOH event at Siriraj Hospital, Thailand, included a retrospective review (events during January - December 2018) and prospective recruitment (events during January 2019 - August 2022). In all cases involving prospective follow-up data, informed consent was obtained from the participants. csPOH patients were managed by a multidisciplinary team including allergists, anesthesiologists, adverse drug reaction (ADR) pharmacists, immunologists, and dermatologists. Eligible patients were identified as csPOH patients by anesthesiologists. Inclusion criteria were any patient aged ≥ 18 years from a procedural unit including surgical units, delivery rooms, and endoscopy units and experiencing a csPOH event. The exclusion criterion was patient refusal to participate in the study. This study was conducted in accordance with the Declaration of Helsinki, and was approved by the institutional review board of the Faculty of Medicine Siriraj Hospital (SIRB), Mahidol University (COA no. Si 020/2019, protocol number 805/2561 (EC4)).

Study definitions

- ***Immediate hypersensitivity reaction (IHR) and perioperative immediate hypersensitivity reaction***

  IHR was defined as the presence of any of the following symptoms including urticaria/angioedema, bronchospasm, or anaphylaxis regardless of whether the underlying mechanisms was allergic or non-allergic. csPOH was defined as IHR occurring during a procedure requiring general anesthesia, regional anesthesia, sedation, or anesthesiologist monitoring, and was classified by degree of severity by the modified Ring and Messmer four-step grading scale.[1] Allergist-diagnosed POH was defined as an adverse event history compatible with POH with culprit agent(s) confirmed by CAE performed by an allergist. Life-threatening POH was defined as grade III or grade IV by modified Ring and Messmer grading scale.

- ***Phase of reaction***

  We classified the timing of the event in relation to the procedure into three phases [adapted from UK 6th National Audit Project, (NAP6)[3]], including before procedure, during the procedure, and after the procedure. This was also applied to general anesthesia. The induction phase before the beginning of the procedure was defined as the transition from awake to anesthetized state. This phase covered all medications including premedication. The maintenance phase during the procedure was defined as the state of being unconscious until awakening. The recovery phase after the end of the procedure was defined as the state of being awakening and transference to the recovery room.

Diagnostic workup for POH

This procedure is the unified diagnostic workup algorithm that we have been using in routine diagnostic workup for csPOH at Siriraj Hospital. All patients experiencing csPOH are invited to have a two-stage diagnostic workup performed, namely initial evaluation, followed by CAE (**Figure 1**). The aim of the initial evaluation is to list all possible causes. The initial evaluation involves taking the history, physical examination, and a structured review of medical records including anesthetic, operative, and medication records. After that, all patients are informed about CAE explaining it is for identifying the definite causes and underlying mechanisms of their POH, and are asked to provide informed consent. CAE consists of skin testing including skin prick tests (SPT) and intradermal tests (IDT), a glove challenge test,

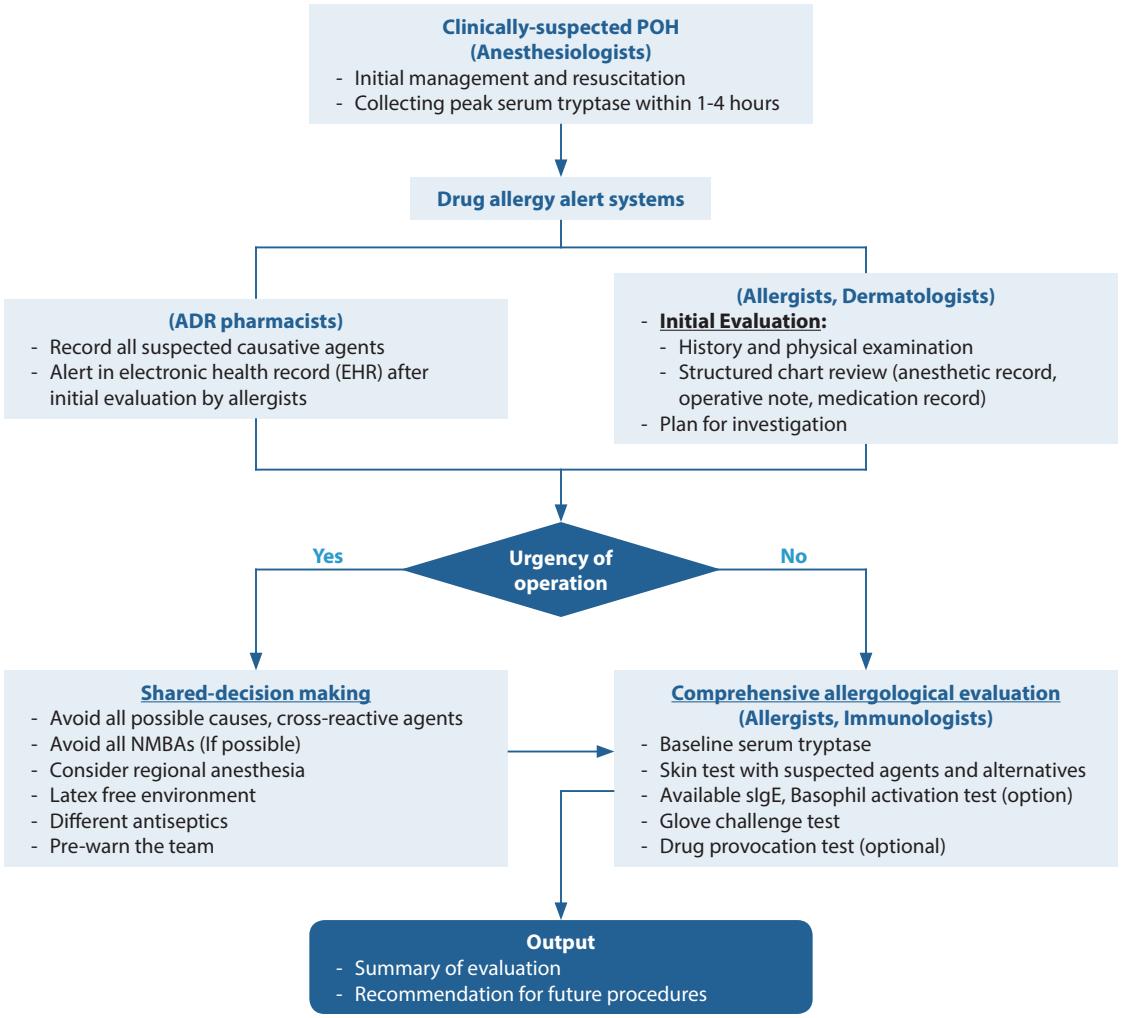

Figure 1. Proposed algorithm for POH investigation.

Abbreviation: POH, perioperative immediate hypersensitivity reaction; ADR, adverse drug reaction unit; NMBA, neuromuscular blocking agent; sIgE, drug-specific immunoglobulin E

and blood sampling for baseline serum tryptase (BST) and specific IgE (sIgE) including latex, chlorhexidine, pholcodine, and quaternary ammonium morphine. Some cases received drug provocation test (DPT) or basophil activation test (BAT).

Comprehensive allergological evaluation tests

- ***Skin tests***

  Skin tests were performed on the volar aspect of the arm to identify the causative agents, potential cross-reactive agents, and safe alternatives for future administration. SPT and IDT were performed using non-irritating concentrations according to the European Academy of Allergy and Clinical Immunology (EAACI) position paper on the investigation of POH and beta-lactams.[1,10] A positive reaction in SPT was defined as a wheal diameter at least 3 mm greater than the negative control together with surrounding flare, appearing after 15 minutes. A positive reaction in IDT was defined as at least a 3 mm in the diameter of the injection papule compared with the initial wheal surrounded by erythema after 20 minutes.[11]

- ***Serum tryptase and specific IgE tests***

  During the POH event, 3 to 5 mL of blood was collected within 1 to 4 hours after onset, and peak serum tryptase was measured. Additional blood tests were collected after resolution of POH for at least 24 hours, and baseline serum tryptase (BST) and sIgE for latex, chlorhexidine, quaternary ammonium morphine, and pholcodine using ImmunoCAP (Phadia AB, Upsala, Sweden) were measured. A positive peak serum tryptase was defined as greater than 1.2 × BST + 2.[12,13] and other alternative cut points were analyzed. A positive sIgE was defined as a titer value of at least 0.35 kU/L.

- ***Basophil activation test (BAT)***

  In high-risk patients, such as patients with severe, uncontrolled cardiovascular or respiratory diseases and patients taking certain medications that might interfere with DPT, BAT was performed to help identify the causative agent(s) and provide safe alternatives. At least 6 mL of blood was collected in an EDTA tube and analyzed for CD63 and CD203c expressing basophils

by flow cytometry. The details of the procedure for BAT used at our center is described in a previous report.[14]

- ***Gloves challenge test with prick-puncture***

  This was performed by wearing a latex-containing glove on one hand, and non-latex gloves on the other hand. The hands were soaked in normal saline, and were worn for 60 minutes. A positive test result was defined as contact erythema and urticaria. Latex powdered gloves, containing latex protein ≤ 200 μg per g (SriTrang® examination gloves, Sri Trang Gloves Company, Bangkok, Thailand) were used for the test.

- ***Drug provocation test (DPT)***

  DPT was performed only in specific patients after complete risk stratification along with skin and blood testing. The aims of the DPT were either to confirm tolerance to certain medications (e.g., antibiotics) because a negative skin test could not completely exclude allergic reactions, or to provide a safe alternative for subsequent administrations. A positive result was defined as the presence of evaluated objective signs of IHR.

Data collection

All demographic data, clinical characteristics of csPOH events, findings of CAE, and patient POH outcomes after CAE were collected from medical records.

Statistical analysis

Analysis was performed descriptively. Continuous data are presented as mean (standard deviation, SD) or as medians (interquartile range, IQR) as appropriate. Categorical data are presented as frequency and percentage. Statistical analysis was performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL).

Results

Incidence of POH stratified by severity

A total of 202,285 procedures requiring anesthesiologist monitoring were performed from 1 January 2018 to 31 August 2022. **Figure 2** summarizes the flow of participants through the study. Of 68 patients identified as csPOH, only 52 were diagnosed as POH by allergist evaluation. In cases without tryptase result or skin rash, we diagnosed anaphylaxis by the NIAID/FAAN Consensus Criteria 2005.[15] The incidence of POH was 1 case per 4,304 procedures. The incidence of life-threatening POH was 1 case in 11,900 procedures. A final number of 41 patients were included for analysis including 35 CAE workups and 6 causative agents identified without CAE because only single agent was administered in the waiting room, before undergoing procedures. (**Figure 2**).

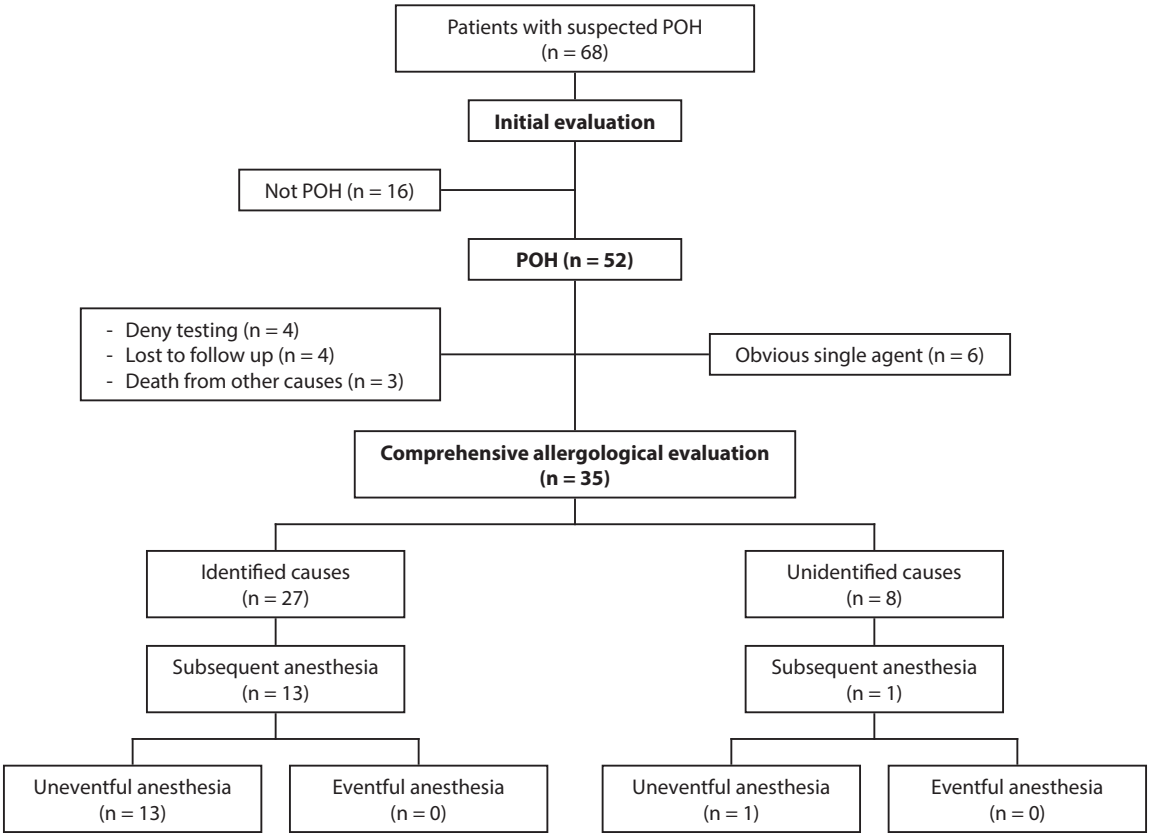

Figure 2. Flow of participants.

Abbreviations: POH, perioperative immediate hypersensitivity reaction

Clinical characteristics

The characteristics of patients and details of POH are summarized in **Table 1**. Of these 41 POH patients, 22 (53.7%) were female. The mean age at POH event was 59.32 years (SD 2.39). Twenty-nine percent of patients had a previous history of drug hypersensitivity before the POH event, of which 12.2% had hypersensitivities to ≥ 2 unrelated drugs (drugs with different structures or pharmacological properties). Asthma (14.6%), and heart disease (14.6%) were the two most common comorbidities. None of the patients had mast cell-related disorders. Most patients had at least one previous procedure before the POH event.

The most common type of anesthesia was general anesthesia (65.9%), followed by regional anesthesia (21.9%) and local anesthesia (12.2%). The proportions of POH reaction by graded severity were 2.4% as grade I, 46.4% as grade II, and 51.2 % as grade III. None of the patients had a grade IV severity event. Thirty-six percent of patients had onset of POH before the procedure, 36.6% during the procedure, and 26.8% after the procedure. Cutaneous manifestations (46.4%) were the first recognized signs, followed by cardiovascular manifestations (36.6%) and respiratory manifestations (17%). However, the overall POH manifestations were cutaneous (82.9%), cardiovascular (78.0%), and respiratory (63.4%).

Table 1. Demographic, epidemiologic, and clinical characteristics of patients with allergist-diagnosed POH (n = 41)

Parameter	Value
Age, mean (SD), y	59.32 (2.39)
Female	22 (53.7)
Medical history	
Drug hypersensitivity	12 (29.3)
• Single drug	7 (17.1)
• ≥ 2 unrelated drugs†	5 (12.2)
• POH settings	3 (7.3)
• Non-POH settings	2 (4.9)
Comorbidities	
• Asthma	6 (14.6)
• Allergic rhinitis/conjunctivitis	3 (7.3)
• Urticaria	4 (9.8)
• Eczema	0 (0.0)
• History of food allergy	2 (4.9)
• Heart disease	6 (14.6)
• Mast cell-related disorder	0 (0.0)
Number of previous procedures	
• None	12 (29.3)
• 1	15 (36.6)
• ≥ 2	14 (34.1)
Characteristics of anesthesia associated with the POH event	
ASA status	
• 1	5 (12.2)
• 2	24 (58.5)
• 3	10 (24.4)
• 4	2 (4.9)
Type of anesthesia	
• GA	27 (65.9)
• RA	9 (21.9)
• LA	5 (12.2)
• MAC	0 (0.0)
Characteristics of POH reaction	
Severity by Modified Ring and Messmer grade*	
• I	1 (2.4)
• II	19 (46.4)
• III	21 (51.2)
• IV	0 (0.0)
Phase of reaction in relation to procedures	
• Before procedure	15 (36.6)
• During procedure	15 (36.6)
• After procedure	11 (26.8)
First recognized manifestation	
• Cutaneous manifestations	19 (46.4)
• Cardiovascular manifestations	15 (36.6)
• Respiratory manifestations	7 (17.0)
• Others	0 (0.0)
Any manifestation during POH event	
• Cutaneous manifestations	34 (82.9)
• Cardiovascular manifestations	32 (78.0)
• Respiratory manifestations	26 (63.4)
• Others	1 (2.4)

Notes: All data are presented as n (%) unless stated otherwise.
†Unrelated drugs: drugs with different structures or pharmacological properties
*Modified Ring and Messmer grading system: grade I, generalized mucocutaneous signs; grade II, mucocutaneous signs and bronchospasm or hypotension (but not life-threatening); grade III, severe life-threatening multi-organ manifestations (arrhythmia, bronchospasm, cardiovascular collapse); grade IV, cardiac arrest.[35]
Abbreviation: ASA, anesthesiologist physical status classification; GA, general anesthesia; LA, local anesthesia; RA, regional anesthesia; MAC, monitored anesthesia care; POH, perioperative immediate hypersensitivity reaction.

Causative agents and their relation to the anesthetic phase

A summary of identified causative agents is shown in **Figure 3**. Antibiotics were the most commonly identified causative agent (14/41 patients; 34.1%), of which cefazolin was the most common antibiotic (10/14 patients; 71.4%). Eight patients (19.5%) had POH events related to either antiseptic or disinfectant (chlorhexidine 4/8, povidone iodine 1/8, and ortho-phthaladehyde (OPA) 3/8). Latex (12.2%) and morphine (12.2%) were the third most common causative agents.

We compared causative agents by phase of reaction in relation to procedures (**Table 2**). The median time before the onset of POH was 10 minutes (5, 20) for intravenously administered medications. None of the identified causative agents was administered subcutaneously, intramuscularly, or intrathecally. Before procedure, cefazolin (53.3%) was the most identified causative agent, followed by morphine (13.3%). Latex (20.0%) and morphine (20.0%) were the two most common causes during procedure. After procedure, the most identified cause was OPA (27.3%), followed by latex (18.2%) and a chlorhexidine (18.2%).

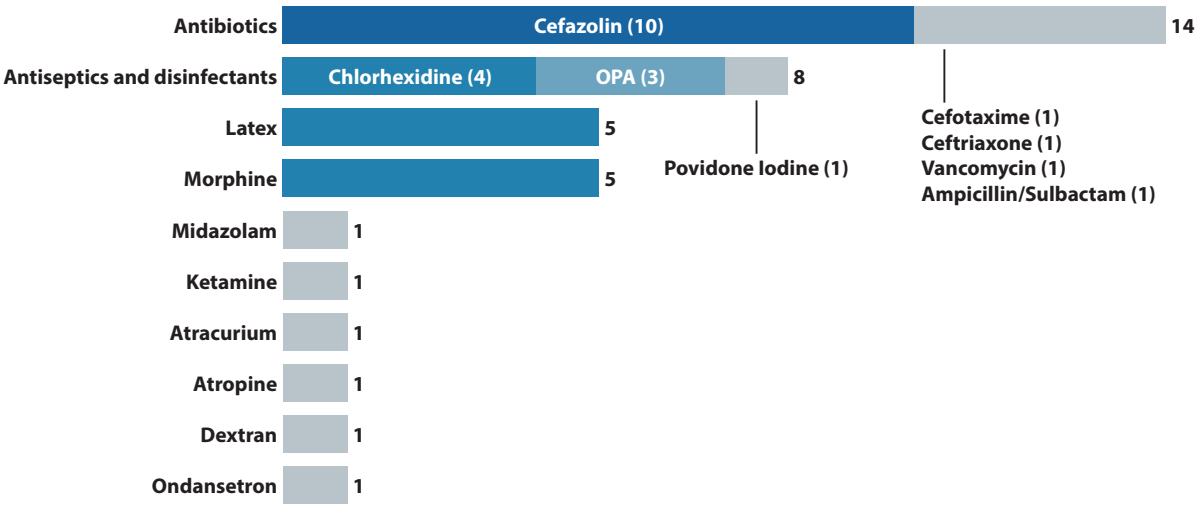

Figure 3. Proportions of identified causative agents.

Abbreviations: OPA, Ortho-phthaladehyde

Table 2. Comparisons of causative agents by phase of reaction in relation to procedures (n = 41)

Agents	Before (n = 15)	During (n = 15)	After (n = 11)
Antibiotics			
• Cefazolin	8 (53.3)	2 (13.3)	0 (0.0)
• Ceftriaxone	1 (6.7)	0 (0.0)	0 (0.0)
• Cefotaxime	0 (0.0)	1 (6.7)	0 (0.0)
• Vancomycin	1 (6.7)	0 (0.0)	0 (0.0)
• Ampicillin/sulbactam	1 (6.7)	0 (0.0)	0 (0.0)
Anesthetic drugs			
• Atracurium	1 (6.7)	0 (0.0)	0 (0.0)
• Midazolam	1 (6.7)	0 (0.0)	0 (0.0)
• Ketamine	0 (0.0)	1 (6.7)	0 (0.0)
• Morphine	2 (13.3)	3 (20.0)	0 (0.0)

Agents	Before (n = 15)	During (n = 15)	After (n = 11)
Antiseptics and disinfectants			
• Chlorhexidine	0 (0.0)	2 (13.3)	2 (18.2)
• Povidone iodine	0 (0.0)	0 (0.0)	1 (9.1)
• Ortho-phthaladehyde	0 (0.0)	0 (0.0)	3 (27.3)
Others			
• Latex	0 (0.0)	3 (20.0)	2 (18.2)
• Ondansetron	0 (0.0)	1 (6.7)	0 (0.0)
• Atropine	0 (0.0)	0 (0.0)	1 (9.1)
• Dextran	0 (0.0)	1 (6.7)	0 (0.0)

Notes: All data are presented as n (%). We classified the timing of event in relation with the procedure into three phases (adapted from UK 6th National Audit Project (NAP6)) including before procedure, during procedure, and after procedure.

Among 12 patients (29.3%) who had never undergone any procedures, latex was the most identified cause of POH while cefazolin was the major cause of POH in 29 patients (70.7%) who had undergone previously uneventful procedures. Cefazolin was usually the causative agent identified among patients with a history of at least one previous procedure. Of these, 60% (6/10) cefazolin-allergic patients previously received cefazolin in the previous procedure while 40% (4/10) patients had no or unknown history of previous cefazolin use. For non-injectable administered medications, POH to chlorhexidine and OPA were also found in patients with a history of previous procedure while POH to latex was found in patients with and without previous procedures (16.6% versus 10.3%, respectively).

Time interval between POH episode and allergist's evaluation

Among 35 patients who had completed CAE, 24 patients (68.6%) were evaluated within the recommended period, that is, between 4 weeks and 4 months after the onset of POH. None of the patients were evaluated within 4 weeks after the POH event. There were 11 patients (31.4%) who were evaluated later than 4 months after POH during the COVID19 pandemic, which delayed allergist evaluation. Among these 11 patients, 4 had positive skin tests upon initial CAE while 6 of 7 patients with initial negative skin tests were evaluated at 4-6 weeks apart. One of 6 patients with retesting yielded positive skin test conversion.

Identified causative agents by comprehensive allergological evaluation

Table 3 summarizes the identified causative agents by CAE. Most causative agents were demonstrated by immediate skin testing by SPT and IDT. Cefazolin and morphine were diagnosed by skin test in 83.3% and 100%, respectively. One cefazolin-allergic patient had a negative skin test result, but a positive reaction during DPT. The reaction exerted during DPT was compatible with anaphylaxis characterized by urticaria, hoarseness, chest tightness, and epinephrine was given. One case had vancomycin-induced severe red man syndrome, which was retrospectively reviewed by an allergist who found that the rate of intravenous infusion was erroneous given as 2 grams within 30 minutes. This patient had a positive serum tryptase test, negative skin tests, and a negative DPT using the optimal infusion rate.

Latex allergy was mainly diagnosed by latex-sIgE. We did not perform latex skin test because it is unavailable in Thailand. One in 5 patients tested (20%) had positive gloves challenge test with prick-puncture. However, we did not use specialized high latex protein content gloves because they are unavailable in Thailand. Chlorhexidine allergy was diagnosed by skin test in 3 of 4 patients tested (75%). One patient had a negative skin test, but positive chlorhexidine-sIgE. We did not perform a chlorhexidine provocation test. All OPA allergies were diagnosed by skin test, using a non-irritating concentration of 5.5 mg/mL for SPT.[16] Two patients had positive BAT for OPA, according to a previous report from our team.[17] Povidone iodine was diagnosed by the strong reaction to SPT in 1 case.

Table 3. Details of identified causative exposures by CAE (n = 28)

Causative agent	N	Duration after exposure, median (interquartile range), min	Positive Results			
			Skin test	sIgE‡	DPT	BAT
IV administration						
• Cefazolin	6	10 (5, 20)	5 (83.3)	NA	1 (100)	0 (0.0)
• Morphine	5		5 (100)	NA	NA	NA
• Ampicillin/sulbactam	1		1 (100)	NA	NA	NA
• Ceftriaxone	1		1 (100)	NA	NA	NA
• Vancomycin	1		0 (0.0)	NA	0 (0.0)	NA
• Midazolam	1		1 (100)	NA	NA	NA
• Atracurium	1		1 (100)	NA	NA	NA
• Ketamine	1		1 (100)	NA	NA	NA
• Atropine	1		1 (100)	NA	NA	NA
• Dextran	1		0 (0.0)	NA	NA	NA

Table 3. (Continued)

Causative agent	N	Duration after exposure, median (interquartile range), min	Positive Results			
			Skin test	sIgE‡	DPT	BAT
IM/SC/intrathecal administration						
• None	NA	NA	NA	NA	NA	NA
Other						
• Latex	5	NA	NA	5 (100)	1 (20)*	NA
• Chlorhexidine	4	NA	3 (75)	1 (100)	NA	NA
• Ortho-phthaladehyde	3	NA	3 (100)	NA	NA	2 (100)
• Povidone iodine	1	NA	1 (100)	NA	NA	NA

Notes: All data are presented as n (%) unless stated otherwise. *Gloves challenge test with prick-puncture was performed by wearing latex-containing glove on 1 hand, and non-latex gloves on another hand. Hands were soaked with normal saline and the gloves were worn for 60 minutes. Contact erythema, urticaria were considered positive result. Latex powdered gloves, containing latex protein ≤ 200 µg per g (SriTrang® examination gloves, Sri Trang Gloves Company, Thailand) were used for the test.
‡Drug-specific IgE using solid-phase immunoassay, ImmunoCAP (Phadia AB, Upsala, Sweden). We tested specific IgE for latex, chlorhexidine, pholcodine, and quaternary ammonium morphine in the cohort.
Abbreviations: BAT, basophil activation test; CAE, comprehensive allergological evaluation; DPT, drug provocation test; sIgE, specific immunoglobulin E; NA, not applicable; IV, intravenous; IM, intramuscular; SC, subcutaneous.

Serum tryptase

Twenty-nine of 41 patients (70.7%) had available peak tryptase. Twenty-two (22/29) peak tryptase samples were collected within the recommended time (1-4 hours after onset of anaphylaxis). The median time of collection was 85 minutes. We further analyzed for positive results using different criteria in grade II-IV POH. Positive proportions using ratio of peak tryptase/BST ≥ 1.5,[18] peak tryptase > 1.2BST + 2 ng/mL,[12,13] Δ tryptase (peak tryptase - BST) > 3 ng/mL, and peak tryptase > 11.4 ng/mL[19] were 68.2%, 59.1%, 59.1%, and 45.5% respectively. The median BST level was 3.34 ng/mL (1.97, 5.17). The maximum BST in our study was 18.4 ng/mL in one patient with end-stage renal disease. We further analyzed for positive allergy testing (included skin tests, sIgE, or DPT/BAT) based on positive tryptase results. By using the consensus formula and Δ tryptase > 3 ng/mL, the proportion of positive results for allergy testing were 10/11 (90.9%) while only 10/13 (76.9%) had positive allergy testing results in the ratio peak tryptase/BST ≥ 1.5.

Outcomes of subsequent anesthesia after allergist evaluation

We prospectively followed our patients who underwent subsequent anesthesia. The median follow-up duration was 2.06 years (1.27, 3.38). Of 35 patients who completed CAE, 27 patients had identified cause while 8 patients had no identified causes. However, subsequent anesthesia was safely performed in 13 patients with identified causes and 1 patient with an unidentified cause. All 14 subsequent anesthesia were uneventful.

Discussion

This is the first report of POH from Thailand with allergist's CAE performed as part of a unified diagnostic workup algorithm for confirming the diagnosis of POH and identifying the culprit agent. The estimated incidence in our center was 1:4,304 for all severities of POH events and 1:11,900 for at least a grade III POH event. A previous multi-centered study in Thailand between 2003 and 2004 reported an incidence of 1:5,500 cases of anesthesia.[9] However, it included cases with a wide range of clinical manifestations, did not perform an allergist's evaluation, and used a different severity grading system, so direct comparison to estimate a temporal trend is not possible. Our POH incidence falls within the range of the global incidence, which has varied between 1:18,600 and 1:353 anesthetic procedures.[20] To accurately estimate spatial and temporal trends in POH incidence, we suggest national or international standardization of methods including definitions to identify eligible cases and to diagnose using allergist's CAE evaluation should be implemented. POH was more prevalent among female (for certain medications), or patients with mast cell disorders, history of atopic diseases (e.g., asthma, eczema, or allergic rhinitis), chronic urticaria/angioedema, or previous history of drug allergy.[21] Elderly patients (age ≥ 65 years), patients undergoing a cardiac procedure, or patients with and comorbid conditions including weight loss, malignancy, paralysis, coagulopathy, renal failure, congestive heart failure, fluid and electrolyte disorder, and neurological disorders were at risk for near-fatal or fatal POH.[4] However, patients with those risk factors were only small proportions in our study. None of the patients was diagnosed with mast-cell disorders. This signified that POH is an unpredictable condition.

Antibiotic was the most commonly identified cause with cefazolin as the leading culprit, which is similar to a recent report from a large tertiary hospital in the United States.[22] Antiseptics, (12.2%), latex (12.2%), and morphine (12.2%) were the joint second leading causes, and chlorhexidine was the most commonly identified antiseptic (9.8%). This was similar to previous reports from the United Kingdom, Denmark, and Belgium (range, 9.0-9.6%).[1] Our data supports the recommendations to include latex and antiseptics, especially chlorhexidine, in the routine POH evaluation as these agents might be hidden culprits.[1,23,24] Interestingly, NMBA was confirmed as the cause of POH in only 1 patient (2.4%), which was different from the previous 2003-2004 Thai report.[9] In other European countries, Australia, New Zealand, and South Korea, NMBAs has been reported to be the first or second most common cause of POH.[25] These differences might be explained by both genetic background and environmental differences, including pholcodine cross-sensitization from antitussive medications.[26] Pholcodine use in Thailand was categorized as category III narcotics, under the Thai Narcotics Act 1994, which permits use as an antitussive medication without prescription.[27] Later in 1996, it was strictly controlled and categorized as category II narcotics.[28] This might have led to a decrease in cross-sensitization to NMBA.

OPA, a disinfectant for flexible endoscopic equipment, was the causative agent in 3 patients (7.3%, 3/41). All of them had reactions during cystoscopy for urinary bladder cancer surveillance. Although contraindications for its use in urinary bladder cancer patients or any repetitive procedures are stated in the package insert as it might increase sensitization risk, cases of OPA-induced allergic reactions have been reported.[17] This agent cannot be completely washed off a cystoscope despite rinsing with water.[29] In the case of POH after endoscopic procedures, we suggested considering OPA as a causative agent and including it in the allergology test panel, which could be either skin tests or BAT.[14,17]

Latex was identified as a causative agent in 5 patients (12.2%). We routinely performed both latex-sIgE and gloves challenge testing in our POH cohort. We did not perform latex skin testing as standardized skin test reagents are unavailable in Thailand. Positive latex-sIgE was demonstrated in all 5 patients while the gloves challenge test was positive in only 1 patient. The glove challenge test at our center was not sensitive, because we do not use specialized, high latex content gloves for testing as these products are unavailable in Thailand. The latex-containing gloves available in our country have low protein content (as low as 50 μg protein/g) in compliance with US Food and Drug Administration Agency regulations.[30] Although the diagnosis of latex allergy by elevated latex-sIgE result alone is not recommended due to potential cross-reactivity from grass or birch pollen sensitization,[31] birch tree species have a temperate climate range and do not grow in tropical countries, such as Thailand, and no birch pollen was found in an airborne pollen survey of Bangkok in between 2012 and 2013.[32] Therefore, we considered positive latex-sIgE as highly probable cases. These cases had no subsequent, recurrent POH reactions during subsequent procedures after assigning a latex-free environment track, which supports the conclusion that latex was the culprit agent.

When categorizing causative agents by phases of reaction in relation to procedures, antibiotics and anesthetic agents accounted for POH events with onset before and during procedures. Both of those types of medication are typically administered early in the operation as infection prophylaxis or an induction agent while antiseptics, disinfectants, and latex caused POH later during and after the procedures. Atropine, which is used to reverse neuromuscular blockade, accounted for POH after the procedures. This may help determine which agents should be included for testing if the broadest testing is limited by local policies or patient-related factors.

We propose a unified diagnostic workup algorithm for POH investigation within a multidisciplinary collaboration in **Figure 1**. An ADR pharmacist and an allergist should be consulted for a patient with suspected POH to perform the initial evaluation by during the hospital admission in which the csPOH event occurred. This step is crucial because it ensures the completeness of the medical records of the event. In case of urgent surgery, the general recommendation for POH is provided as the following: 1) perform the procedure in a latex-free environment, 2) avoid all NMBAs if any NMBA was listed as a potential cause and structurally-related medications, and 3) use a different class of antiseptics if any antiseptic was listed as a potential cause. Substitution of anesthetic agents and analgesics is recommended based on NAP6 recommendations.[33] For elective surgery, if the procedure can be postponed, all patients should urgently undergo CAE which usually is 4-16 weeks after the csPOH event. We suggest performing CAE at 4 weeks because early follow-up and minimizing the number of hospital visits can diminish the loss follow-up rate. The total time for complete evaluation usually takes less than 2-3 months. This protocol was first established in Thailand, and could possibly assist other centers in promptly setting up a workflow for POH patients, initiating the collaboration between specialties, and expanding collaboration between centers for cases referral.

To identify the causative agent(s), skin testing is important and useful tool to confirm evidence of sensitization. It may also be useful for predicting cross-reactions among anesthetic medications, especially NMBAs. Of the 28 patients with a confirmed causative agent in the present study, 82% had positive skin tests, and only 3.6% had a negative skin test followed by a positive reaction by DPT. Furthermore, none of our patients had systemic reactions due to skin tests including the glove challenge test. This suggests skin testing may be a good and safe diagnostic tool in POH.

During the Coronavirus disease 2019 pandemic, we could not perform CAE in recommended time due to the additional burden to our hospital services. We had 11 patients who underwent late skin testing. Four of those 11 (36.4%) patients had positive skin test reactions upon initial skin testing, but the majority had a negative result. We performed subsequent skin testing in 6 of the 7 patients with negative initial skin testing results at 4-6-week intervals,

and we found 1 of the 6 patients (16.7%) had positive conversion. We performed shared decision making as to how to proceed with the other 5 patients with negative skin tests after retesting at 4-6 week intervals, and proceeded to available drug provocation testing. One of these patients had a positive reaction from cefazolin. DPT should be carefully performed and closely monitored. The false negative rate due to the late skin test was 20%. Although retesting after an initial negative skin test might yield a significant additional positive conversion, we would like to emphasize the importance of skin testing within the recommended time to avoid unnecessary and more invasive procedures like DPTs as rare fatality have been reported from re-sensitization even in prior DPT-negative cases.[34]

Paired peak-baseline serum tryptase levels are also crucial to help confirm the diagnosis of anaphylaxis.[13] In our study, only 22 samples (53.7%) were properly collected for peak serum tryptase measurement (within 1-4 hours after onset).[2] We included at least grade II POH for comparative analysis of diagnostic performance according to a 2012 consensus statement.[12] In the present study, 15 of 29 performed paired peak-baseline serum tryptase test results (68.2%) were positive if defined as a ratio peak tryptase/BST ≥ 1.5;[18] 13 of 29 (59.1%) results were positive if defined as the consensus formula and Δ tryptase > 3 ng/mL; and 10 of 11 (90.9%) were positive if defined as either the consensus formula or Δ Tryptase > 3 ng/mL. This implies elevated tryptase might indicate IgE-mediated reactions. Interestingly, 1 patient with severe vancomycin-induced redman syndrome also had elevated tryptase in our case series, indicating that non-IgE-mediated reactions can be associated with elevated serum tryptase.

Thirty-five patients underwent CAE in our center. Fourteen patients (13 identified cause, and 1 unidentified cause) underwent subsequent anesthesia (**Figure 2**). All of them had uneventful subsequent anesthesia. Banerji, et al. reported that 78 of 85 (92%) POH patients that completed the CAE could tolerate subsequent anesthesia.[7] We emphasize the importance of allergist consultation and referral within the appropriate timeframe. Over-labeling or mislabeling of causative agents might occur in the setting without CAE. Complete records, collaboration among the multidisciplinary team, and comprehensive evaluation provides safe subsequent procedures for patients with POH.

The present study has strengths and limitations. The main strength is that this is the first report of an algorithmic multidisciplinary team approach to effective management of POH in Thailand after the EAACI published a position paper on the POH investigation in 2019 and called for collaboration among specialists.[1,31] We have been performing CAE since 2018, developing and refining a proper POH investigations workflow appropriate for the setting of Thailand. It is important to note that we used 'mainly' skin tests and drug provocation tests, and we could identify causative agents in the majority of cases. This means that it would be 'preliminary practical' for allergists in many centers where *in vitro* facilities or advanced drug provocation tests are not available. However, our case series consists of data from only one referral center and adult patients with csPOH. Therefore, the present study may not reflect the true POH incidence in Thailand, and does not include pediatric patients with csPOH. We suggest national collaboration to establish POH investigation guidelines, a nationwide database, and inclusion of pediatric cases are needed in the future studies. We still look for future studies/feedback from our country to assess the appropriateness of this protocol in the future.

Conclusion

Complete records, collaboration among a multidisciplinary team, and comprehensive allergist's evaluation can provide safe subsequent procedures for patients with POH. National and international collaboration to establish POH investigation guidelines and a Thai national database including pediatric patients need to be informed by future studies.

Acknowledgement

The authors gratefully acknowledged Dr. Anthony Tan for English language check.

Conflict of interest declarations

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

Funding disclosure

This was an unfunded study.

References

1. Garvey LH, Ebo DG, Mertes PM, Dewachter P, Garcez T, Kopac P, et al. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. Allergy. 2019;74(10):1872-84.
2. Garvey LH, Dewachter P, Hepner DL, Mertes PM, Voltolini S, Clarke R, et al. Management of suspected immediate perioperative allergic reactions: an international overview and consensus recommendations. Br J Anaesth. 2019;123(1):e50-e64.
3. Cook TM, Harper NJN, Farmer L, Garcez T, Floss K, Marinho S, et al. Anaesthesia, surgery, and life-threatening allergic reactions: protocol and methods of the 6th National Audit Project (NAP6) of the Royal College of Anaesthetists. Br J Anaesth. 2018;121(1):124-33.
4. Gonzalez-Estrada A, Campbell RL, Carrillo-Martin I, Renew JR, Rank MA, Volcheck GW. Incidence and risk factors for near-fatal and fatal outcomes after perioperative and periprocedural anaphylaxis in the USA, 2005-2014. Br J Anaesth. 2021;127(6):890-6.
5. Reitter M, Petitpain N, Latarche C, Cottin J, Massy N, Demoly P, et al. Fatal anaphylaxis with neuromuscular blocking agents: a risk factor and management analysis. Allergy. 2014;69(7):954-9.
6. Gibbs NM, Sadleir PH, Clarke RC, Platt PR. Survival from perioperative anaphylaxis in Western Australia 2000-2009. Br J Anaesth. 2013;111(4):589-93.
7. Banerji A, Bhattacharya G, Huebner E, Fu X, Camargo CA, Jr., Guyer A, et al. Perioperative Allergic Reactions: Allergy Assessment and Subsequent Anesthesia. J Allergy Clin Immunol Pract. 2021;9(5):1980-91.
8. Charuluxananan S, Sriraj W, Punjasawadwong Y, Pitimana-aree S, Lekprasert V, Werawatganon T, et al. Perioperative and Anesthetic Adverse events in Thailand (PAAd Thai) incident reporting study: anesthetic profiles and outcomes. Asian Biomedicine. 2017;11(1):21-32.
9. Thienthong S HT, Pulnitiporn A. The Thai Anesthesia Incidents Study (THAI Study) of Perioperative Allergic Reactions. J Med Assoc Thai. 2005;88:S128-33.
10. Romano A, Atanaskovic-Markovic M, Barbaud A, Bircher AJ, Brockow K, Caubet JC, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams - an EAACI position paper. Allergy. 2020;75(6):1300-15.

11. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy. 2002;57(1):45-51.
12. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol. 2012;157(3):215-25.
13. Vitte J, Amadei L, Gouitaa M, Mezouar S, Zieleskiewicz L, Albanese J, et al. Paired acute-baseline serum tryptase levels in perioperative anaphylaxis: An observational study. Allergy. 2019;74(6):1157-65.
14. Srinoulprasert Y, Rerkpattanapipat T, Sompornrattanaphan M, Wongsa C, Kanistanon D. Clinical value of in vitro tests for the management of severe drug hypersensitivity reactions. Asia Pac Allergy. 2020;10(4):e44.
15. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.
16. Sokol WN. Nine episodes of anaphylaxis following cystoscopy caused by Cidex OPA (ortho-phthalaldehyde) high-level disinfectant in 4 patients after cytoscopy. J Allergy Clin Immunol. 2004;114(2):392-7.
17. Sompornrattanaphan M, Kanistanon D, Srinoulprasert Y, Udnaen S, Jongjarearnprasert K, Wongsa C, et al. Ortho-phthalaldehyde-Induced Anaphylaxis After Cystoscopy: Confirmation by the Basophil Activation Test. J Investig Allergol Clin Immunol. 2020;30(5):365-7.
18. Wongkaewpothong P, Pacharn P, Sripramong C, Boonchoo S, Piboonpocanun S, Visitsunthorn N, et al. The utility of serum tryptase in the diagnosis of food-induced anaphylaxis. Allergy Asthma Immunol Res. 2014;6(4):304-9.
19. Srisuwatchari W, Tacquard CA, Borushko A, Viville S, Stenger R, Ehrhard Y, et al. Diagnostic performance of serial serum total tryptase measurement to differentiate positive from negative allergy testing among patients with suspected perioperative hypersensitivity. Clinical & Experimental Allergy. 2022;52(2):334-44.
20. Harper NJN, Cook TM, Garcez T, Farmer L, Floss K, Marinho S, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). Br J Anaesth. 2018;121(1):159-71.
21. Caffarelli C, Stringari G, Pajno GB, Peroni DG, Franceschini F, Dello Iacono I, et al. Perioperative allergy: risk factors. Int J Immunopathol Pharmacol. 2011;24(3 Suppl):S27-34.
22. Kuhlen JL, Jr., Camargo CA, Jr., Balekian DS, Blumenthal KG, Guyer A, Morris T, et al. Antibiotics Are the Most Commonly Identified Cause of Perioperative Hypersensitivity Reactions. J Allergy Clin Immunol Pract. 2016;4(4):697-704.
23. Chiewchalermsri C, Sompornrattanaphan M, Wongsa C, Thongngarm T. Chlorhexidine Allergy: Current Challenges and Future Prospects. J Asthma Allergy. 2020;13:127-33.
24. Sompornrattanaphan M, Kreetapirom P, Srinoulprasert Y, Kanistanon D, Klinniyom A, Wongsa C, et al. Severe anaphylaxis after pelvic examination: a case report of dual latex and chlorhexidine allergies. Allergy Asthma Clin Immunol. 2019;15:19.
25. Mertes PM, Ebo DG, Garcez T, Rose M, Sabato V, Takazawa T, et al. Comparative epidemiology of suspected perioperative hypersensitivity reactions. Br J Anaesth. 2019;123(1):e16-e28.
26. Florvaag E, Johansson SG. The pholcodine story. Immunol Allergy Clin North Am. 2009;29(3):419-27.
27. Gazette RTG. Ministerial Regulations issued under the Psychotropic Substance Act No. 11 (B.E. 2537) 1994 [Available from: http://www.ratchakitcha.soc.go.th/DATA/PDF/2537/A/064/48.PDF.
28. Gazette RTG. Ministerial Regulations issued under the Psychotropic Substance Act No. 135 (B.E. 2539) 1996 [Available from: http://www.ratchakitcha.soc.go.th/DATA/PDF/2539/E/023/8.PDF.
29. Miner N, Harris V, Lukomski N, Ebron T. Rinsability of orthophthalaldehyde from endoscopes. Diagn Ther Endosc. 2012;2012:853781.
30. Cornish K, M. Bates G, Slutzky JL, Meleshchuk A, Xie W, Sellers K, et al. Extractable Protein Levels in Latex Products and their Associated Risks, Emphasizing American Dentistry. Biology and Medicine. 2019;11(2).
31. Garvey LH, Ebo DG. Perioperative Hypersensitivity Reactions: Time for Collaboration. J Allergy Clin Immunol Pract. 2021;9(5):1992-3.
32. Songnuan W, Bunnag C, Soontrapa K, Pacharn P, Wangthan U, Siriwattanakul U, et al. Airborne pollen survey in Bangkok, Thailand: A 35-year update. Asian Pac J Allergy Immunol. 2015;33(3):253-62.
33. Harper NJN, Cook TM, Garcez T, Lucas DN, Thomas M, Kemp H, et al. Anaesthesia, surgery, and life-threatening allergic reactions: management and outcomes in the 6th National Audit Project (NAP6). Br J Anaesth. 2018;121(1):172-88.
34. Sompornrattanaphan M, Wongsa C, Kreetapirom P, Taweechue AJ, Theankeaw O, Thongngarm T. Fatal anaphylaxis from a second amoxicillin/clavulanic acid provocation after a prior negative provocation. J Allergy Clin Immunol Pract. 2020;8(2):752-4.
35. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet. 1977;1(8009):466-9.