Atopy, allergy and allergens in the perioperative setting

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Summary

Hypersensitivity reaction is a generic term for every unexpected, reproducible reaction after exposure to a certain substance that goes beyond the expected effect and does not occur in healthy patients. Perioperative hypersensitivity reactions (POH) are rare events but are associated with significant morbidity and mortality. POH can be immunological or non-immunological, differentiation based on clinical symptoms alone is not possible. There are 4 degrees of severity of hypersensitivity reactions. Grade 3 and 4 reactions are called anaphylaxis. A previous unexplained hypersensitivity reaction during general anaesthesia is the main risk factor for the occurrence of a POH. Typical prodromes may be absent under general anaesthesia, or the symptoms may be masked by the effects of anaesthesia and surgery. Hypotension, the most common initial symptom of perioperative anaphylaxis, also regularly occurs during uncomplicated anaesthesia. Especially during the induction phase of anaesthesia, several substances are administered in a short space of time. For these reasons, both the diagnosis of POH and the identification of the causative agent may be difficult. The most common triggers of POH are muscle relaxants and antibiotics. A favourable outcome of life-threatening perioperative anaphylaxis depends on the timely diagnosis and the prompt initiation of adequate therapeutic measures. Fluid resuscitation with crystalloid solutions and treatment with epinephrine are the most important aspects of initial therapy. In contrast, antihistamines and glucocorticoids are of limited value in the acute management of anaphylaxis. The diagnostics after POH aim to secure or rule out the diagnosis and identify the trigger and safe alternatives for future anaesthesia. Key components include the serological determination of mast cell tryptase and an allergological step-by-step evaluation. Interdisciplinary cooperation between anaesthesia and allergology is of vital importance.

Introduction

Perioperative hypersensitivity reactions (POH) are rare, but serious anaesthesiological complications. A positive outcome following severe POH is significantly dependent on **early recognition** and **prompt initiation of appropriate treatment**. At the same time, physiologic responses to anaesthesia and surgery may mask the diagnosis. Profound knowledge of the underlying pathophysiology, clinical presentation and major components of emergency treatment together with heightened awareness are therefore essential for those practicing anaesthesiology.

Pathophysiology

Hypersensitivity reaction is an umbrella term for any unexpected, reproducible reaction following exposure to a specific substance, which exceeds the expected effect, and which does not occur in the healthy [1].

Conflicts of interest
The author declares no competing interests.

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Hypersensitivity – Anaphylaxis – Allergy – Epinephrine – Mast Cell Tryptase

Based on the underlying pathomechanism, hypersensitivity reactions can be divided into immune-mediated allergic reactions and non-immunological non-allergic reactions [2].

Approximately 60–70 % of POH are the result of specific **immunological mechanisms** [2,3]. The Coombs and Gell classification divides allergic reactions into types I–IV. Those reactions relevant to the perioperative phase are typically type I reactions, which are generally IgE-mediated [4]. An initial contact with the allergen leads to so-called **sensitisation.** In effect, **allergen-specific antibodies** are produced in plasma cells at this stage, going on to bind to the surface receptors of mast cells and basophils. Renewed contact with the allergen leads to a **type I** – also known as **immediate type** – **allergic reaction:** the allergen binds to specific IgE antibodies on mast cells and basophils leading to cross-linking of neighbouring IgE antibodies and activation of effector cells [1,5].

In contrast, approximately 30 % of POH are of non-allergic aetiology. The underlying mechanisms include

- unspecific activation of **mast cells** and **basophils** by IgE-independent stimuli,
- activation of the **complement system,** and
- dysfunction of **arachidonic acid metabolism.**

As opposed to allergic POH, non-allergic POH does not result in a specific immune response [3,6]. The latter is **neither dose-dependent nor does it require prior sensitisation;** the severity is typically less pronounced. However, it is impossible to distinguish between allergic and non-allergic POH on the basis of clinical presentation [6].

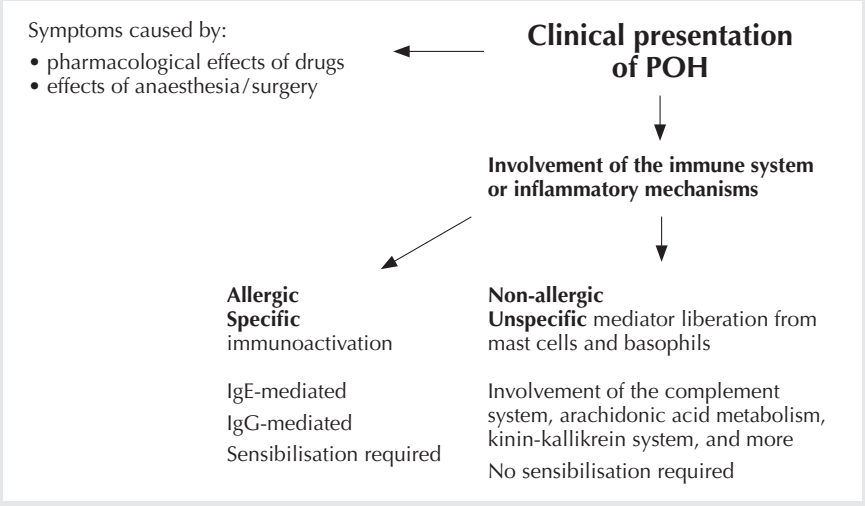
It is impossible to distinguish between allergic and non-allergic POH on the basis of clinical presentation alone (Fig. 1).

In both conditions, the activation of mast cells and basophils leads to degranulation and liberation of various **mediators** (including histamine, tryptase, leukotrienes, proteoglycans, arachidonic acid metabolites, thrombocyte activating factor, cytokines such as tumour necrosis factor α). Amongst other things, these affect the **capillary permeability** and smooth muscle of various organ systems, effecting pathophysiologic changes of the

- **skin** (urticaria, angioedema),
- **gastrointestinal tract** (cramps, nausea, vomiting, diarrhoea),
- **cardiovascular system** (hypotension, tachycardia, arrhythmia), and
- **respiratory tract** (bronchoconstriction, airway obstruction) [7,8].

The severity of hypersensitivity reactions can be graded using the Ring and Messmer classification, which defines a scale of 1 to 4 (Tab. 1).

Figure 1



Pathomechanism underlying POH (modified based on [6]). **POH:** perioperative hypersensitivity reaction; **IgE:** immunoglobulin E; **IgG:** immunoglobulin G.

Table 1

Severity grading scale for hypersensitivity reactions (modified based on [14]).

Grade		Dermal/General Signs & Symptoms	Gastrointestinal Tract	Respiratory Tract	Cardiovascular System
I	**Isolated dermal reaction**	Pruritus Urticaria Flush Angioedema	–	–	–
II	**Moderate involvement of the cardiovascular and/or respiratory system**	Pruritus Urticaria Flush Angioedema	Nausea Vomiting Cramps	Rhinorrhoea Hoarseness Dyspnoea	Tachycardia Hypotension Arrhythmia
III	**Life-threatening involvement of the cardiovascular and/or respiratory system**	Pruritus Urticaria Flush Angioedema	Vomiting Defecation	Laryngeal oedema Bronchospasm Hypoxia/cyanosis	Shock
IV	**Maximum severity: cardiorespiratory arrest**	Pruritus Urticaria Flush Angioedema	Vomiting	Respiratory arrest	Cardiac arrest

Anaphylaxis is a sudden onset, life-threatening, generalised hypersensitivity reaction (grade III / IV), which may be triggered by an allergic or non-allergic stimulus [9].

In anaphylactic shock, mediator associated peripheral vasodilation with reduced systemic vascular resistance and increased capillary permeability lead to volume redistribution through extravasation. The reduction in intravascular fluid load results in reduced ventricular filling, leading to compensatory tachycardia. When cardiac output can no longer be maintained, distributive shock sets in [5]. As a result of the reduced perfusion pressure, coronary blood flow and with that myocardial contractility are impaired. These mechanisms contribute to ongoing haemodynamic shock. Fluid sequestration may lead to oedema of the airways, complicating airway management. Bronchospasm may develop, predisposing additionally to hypoxia.

Epidemiology

Whilst POH is an uncommon occurrence, it is associated with significant morbidity and mortality [4]. There is noticeable heterogenicity in published data with significant geographic variations with regard to incidence and mortality of the condition [6,7]. Larger European retrospective studies undertaken in the past few years indicate an incidence of approximately 1:10,000 [10,11]. The lack of standardised reporting tools and a uniform definition of POH makes it seem likely, however, that the incidence is underreported; low grade reactions are often not documented at all. The mortality in Europe of between 4 and 9 % is significant [2,12,13]. Perioperative anaphylaxis is responsible for between 5 and 7 % of all deaths during anaesthesia [3].

There is significant geographic variation with regard to the most common triggers of POH. In summary, antibiotics are the most common trigger of POH in the USA, Denmark and Spain, whilst in most other European countries and Australia the majority of POH are caused by neuromuscular blocking agents [3,13]. A trend towards a relative increase in POH caused by antibiotics and a reduction in those reactions caused by natural latex has been documented.

As a result of the infrequent occurrence of POH and the more or less "random" character of any emergence there is insufficient data and poor evidence for any therapeutic intervention. The potential for a fatal outcome precludes the existence of any randomised controlled trials. Available recommendations are instead based on retrospective analyses, small case series and case reports in addition to pathophysiological considerations and expert opinions [7].

Risk Factors

Risk factors for developing POH

In general, women are affected by POH three times more often than men [11, 13]. Available data puts the peak age at between 10 and 50 years [11].

The most important risk factor for developing POH is a history of a previous immediate type hypersensitivity reaction during general anaesthesia, especially in those cases where that incident was not the subject of diagnostic follow-up [4].

Equally, the risk of developing POH is increased in those cases in which there is a known allergy to drugs and other substances typically used in the perioperative phase [3].

Atopy describes a genetically determined predisposition to develop

- IgE-mediated hypersensitivity to common allergens (e.g. food allergies),
- allergic rhinitis, and
- allergic bronchial asthma.

In and of itself atopy is not a risk factor for developing an IgE-mediated hypersensitivity reaction to drugs.

However, for certain allergens – and especially for latex – a correlation with atopic disease has been shown [4].

Risk factors for developing severe POH

Advanced age, American Society of Anesthesiology (ASA) category ≥ III and relevant comorbidities are risk factors for an unfavourable disease course when POH occurs. On the one hand this includes immunological disease (such as clonal mast cell disorders, hereditary angioedema), but on the other also obesity, inadequately controlled bronchial hyperresponsiveness and cardiovascular disease, especially coronary artery disease (CHD) [4,10,14]. This is explained by the poor ability of those with cardiovascular disease to compensate the haemodynamic changes which occur with POH, exposing them to a greater risk of shock refractory to treatment. Concurrent treatment with β-blockers and ACE inhibitors also increases the risk for severe POH; patients taking β-blockers not only liberate a greater quantity of mediators but at the same time are unable to develop compensatory tachycardia to counter vasodilation developing in the context of POH [4,7,10]. In addition to the above patient-specific risk factors, delayed administration of epinephrine for the treatment of POH is a further important risk factor for a poor outcome [2].

Clinical Characteristics of Hypersensitivity Reactions in the Context of Anaesthesia

In approximately 80 % of all cases, POH manifests itself during or immediately following induction of anaesthesia as an immediate type reaction within minutes of exposure to the trigger [10].

The kinetics and course of the reaction are significantly related to the route of administration of the trigger substance. Most substances used in the perioperative phase are administered intravenously,

which predisposes to a more rapid onset and greater severity of POH [7]. However, delayed reactions may occur up to 1 hour after administration of the trigger substance, following exposure via the dermal or mucosal routes for example [2,11]. **Induction of anaesthesia** requires that numerous substances are administered in close succession, which can complicate identification of the trigger substance [3]. In addition, the prodromal stage of the hypersensitivity reaction (discomfort, blurred vision, dizziness, hoarseness or dysphagia) is often lacking in this setting. Mild reactions limited to an individual organ system may resolve spontaneously and as such often go unnoticed. Future reexposure to the trigger substance, however, is associated with an increased risk of severe POH.

In a perioperative setting, **higher grade POH** (anaphylaxis) generally manifests itself initially as hypotension with or without tachycardia [10,13]. That entity, however, is unspecific in the setting of anaesthesia induction, with numerous (more likely) differential diagnoses. This may complicate the diagnosis of POH. As such, appropriate vigilance on the part of the anaesthesiologist is of great importance.

Pathophysiological changes occurring during anaesthesia and surgery can mask the diagnosis of POH.

Patient-individual factors also influence the initial manifestation of POH. Bronchospasm, for example, is more likely to occur in patients with (possibly poorly controlled) bronchial hyperresponsiveness (including bronchial asthma, chronic obstructive pulmonary disease (COPD) and obesity) [7,10,15].

Dermal manifestations in the shape of urticaria, flush and pruritus occur in >90 % of patients experiencing a hypersensitivity reaction but may be difficult to discern in the perioperative setting as sedated patients, for example, may not be able to report pruritus and sterile drapes may obscure any otherwise visible skin changes [3]. In severe POH especially, dermal manifestations may initially be lacking entirely as inadequate perfusion sets in, appearing at a later stage following haemodynamic stabilisation [6,9,13].

Differential Diagnoses for POH

The most common differential diagnoses for POH are summarised in Tab. 2. The typical first sign of higher grade POH, namely **hypotension requiring vasopressor therapy**, is also a very common side effect of even uncomplicated neuraxial, general or combined anaesthesia [9,16]. However, at the latest, **failure to respond** to "standard treatment" for hypotension should prompt the anaesthesiologist to consider less common differential diagnoses such as POH.

Isolated **bronchospasm** is typically non-allergic in origin, and more likely to be the consequence of unspecific mechanical (e.g. endotracheal intubation) or pharmacological (e.g. drug induced histamine liberation) triggers in the presence of uncontrolled bronchial hyperresponsiveness. **Bronchospasm in the presence of hypotension**, however, raises suspicion for anaphylaxis, especially in cases where standard treatment fails to resolve the situation and/or unexpected cardiovascular collapse ensues [13].

Surgical complications and **comorbidities** can resemble the clinical presentation associated with hypersensitivity reactions. Furthermore, some drugs may lead to signs and symptoms similar to those seen in POH when they are administered too rapidly or overdosed (e.g. oxytocin).

POH Triggers: Significance of Individual Substances/Substance Groups

Neuromuscular blocking agents (NMBs)

NMBs are amongst the most common triggers of POH. The prevalence is subject to significant **geographical variations**, however [17]: whilst in the USA approximately 11 % of POH are caused by NMBs, at around 50–60 % the proportion is significantly higher in Europe and Australia [18]. The magnitude of

Table 2
Differential diagnoses for POH (modified based on [2] and [6]).

Surgical complications	Haemorrhage, haemorrhagic shock Septic shock BCIS Pulmonary embolism, pneumothorax ACS, tachyarrhythmia, pericardial tamponade Amniotic fluid embolism Mesenteric traction syndrome
Anaesthesiological complications	Relative overdose of anaesthetics Sympathicolysis/vasodilation as a result of neuraxial anaesthesia Superficial anaesthesia Laryngo-/bronchospasm, oedema due to mechanical manipulation of the airway Aspiration
Comorbidities	Bronchial hyperresponsiveness (asthma, COPD, smoking) CHD Mastocytosis Hereditary angioedema Malignant hyperthermia Carcinoid Pheochromocytoma
Pharmacological effects/Drug interactions	Malignant neuroleptic syndrome Serotonin syndrome ACE-induced angioedema

BCIS: bone cement implantation syndrome; **ACS:** acute coronary syndrome; **COPD:** chronic obstructive pulmonary disease; **KHK:** coronary heart disease; **ACE:** angiotensin converting enzyme.

geographical variation even in ethnically comparable regions suggests the influence of **environmental factors** on the prevalence of POH triggered by NMBs. Numerous hypotheses have been put forward; one plausible explanation could be differences in the exposure to substances containing substituted ammonium groups [11]. Quaternary ammonium ions and tertiary amines are contained in the epitope of those NMBs which trigger hypersensitivity reactions. They are also contained in a multitude of **cosmetics, cleaning products** and **disinfectants.** A study looking into IgE-reactivity to quaternary ammonium ions across various occupations found significantly increased reactivity in hairdressers [19,20]. Exposure to these substances could be a possible explanation for the fact that IgE-mediated POH can be triggered in the context of the first exposure to an NMB [7,19]. Substituted ammonium groups are also contained in certain **pharmaceuticals.** Differing exposure to the antitussive drug **pholcodine** is discussed in literature as a possible explanation for regional differences in the prevalence of POH triggered by NMBs [17,21]. Pholcodine is a weak opioid which contains quaternary ammonium ions with significant IgE-sensitising potential in its allergenic epitopes. A discrepancy was noted in the rate of anaphylactic reactions to NMBs in Scandinavian countries in 2005: in Norway – where at the time pholcodine was available over the counter – a high rate of sensitisation and perioperative anaphylactic reactions to NMBs was noted. At the same time, however, in Sweden – where pholcodine was not available – the rate was exceedingly low. As a consequence, pholcodine was taken off the Norwegian market in 2007. The prevalence of sensitisation and anaphylaxis following administration of NMBs subsequently fell significantly [18,22]. A causal link has not been proven to this day, and the pathomechanism by which exposure to pholcodine influences the prevalence of POH triggered by NMBs remains unclear.

Looking at the **allergenic potential** of individual NMBs, the incidence of POH – in relation to the number of exposures – seems to be higher for **succinylcholine** and **rocuronium** than for other substances [13,21]. Cross-reactivity with other NMBs is possible and are not limited to specific chemical classes. Cisatracurium is the substance with the lowest allergenic potential and the smallest risk of cross-reactivity with other NMBs [13,17].

The question of whether anaphylaxis related to **rocuronium** can be influenced positively by administration of **sugammadex** is the subject of controversial debate with opposing positions found in current literature. A plausible molecular mechanism for such an effect has yet to be described. Molecular models show that the allergenic epitopes – that is the ammonium ions of rocuronium – are still available for binding IgE-antibodies after complexation of rocuronium with sugammadex. Individual case reports describing a positive influence of sugammadex on POH trigged by rocuronium are opposed by other research which shows no influence of sugammadex on the course of POH. As such, based on current data, sugammadex use in rocuronium-induced POH is not recommended [13].

Antibiotics

Antibiotics are also amongst the most common triggers of POH, with allergies to **β-lactam antibiotics,** and especially penicillin, being most widespread. 8–12 % of all patients claim to be allergic to penicillin, making penicillin allergy the most common drug allergy elicited from patients [23,24]. In 95 % of those claiming penicillin allergy, however, allergy testing provides no evidence of any such response [23]. This false positive "label" can have far reaching consequences as cephalosporins are routinely used in perioperative antibiotic prophylaxis (PAP). Guidelines recommend **cefazoline,** a 1st generation cephalosporin, as the first choice for most surgical interventions as it is well studied and shows good efficacy against the spectrum of pathogens typically associated with perioperative wound infections, whilst exhibiting a favourable side effect profile and high cost efficiency [25]. However, patients claiming penicillin allergy are more likely to receive a **second-line antibiotic** (e.g. clindamycin, vancomycin) for PAP [23]. These substances are less effective in reducing perioperative infections, whilst also being less well tolerated. In addition, the use of second-line treatment increases the use of broad spectrum antibiotics and as such the **risk of antibiotic resistance** [26].

The possible risk of **cross-reactivity** with other β-lactam antibiotics is the reason for foregoing the use of cefazoline in patients with a history of penicillin allergies. Earlier studies performed in the 1960s and 1970s showed cross-reactivity rates of 8–18 % [23,25]. These high rates were most likely explained by the production of β-lactam antibiotics using a fungal strain, making **contamination** common. However, β-lactam antibiotics have been produced synthetically since the 1980s, such that a significantly lower rate of cross-reactivity may be expected. A meta-analysis published in 2021 showed a rate of cross-reactivity between penicillins and cefazoline of 0.7 %, rising to 3 % in those with proven penicillin allergies [25]. Current knowledge shows that in contrast to previous thinking, cross-reactivity between penicillins and cephalosporins is usually not related to the β-lactam ring but rather to the R1 side chain of the β-lactam molecule. This side chain differs in cefazoline when compared with all other β-lactam antibiotics, so that cefazoline allergy is typically isolated to that substance [23]. As such, available data suggest it is safe to administer cefazoline for PAP to the large majority of patients with putative penicillin allergy. Patients with allergological evidence of penicillin allergy or a history of severe hypersensitivity reactions may be the exception to the rule [25].

Cefazoline can be used safely for PAP in the majority of patients with penicillin allergy.

Unnecessary use of reserve antibiotics for PAP should be reduced through a thorough preoperative evaluation which

details the **type of previous reaction,** differentiating IgE-mediated hypersensitivity reactions from those of other aetiologies and unspecific side-effects. Symptoms such as

- maculopapular exanthema,
- gastrointestinal symptoms,
- isolated pruritus or dizziness and
- headache

are **not suggestive of an IgE-mediated reaction** to penicillin. In contrast, presence of

- urticaria,
- angioedema,
- respiratory tract oedema,
- bronchospasm or
- other signs of anaphylaxis

is **suggestive of a true allergic reaction.** To exclude IgE-mediated reactions and possible cross-reactivity to other β-lactam antibiotics, these cases should be subject to **allergological diagnostics** prior to undertaking further surgery whenever possible. **Preanaesthesia assessment** should include the time since the last hypersensitivity reaction to penicillin; no evidence of sensibilisation remains after 5 years in 50 % of patients who suffered an IgE-mediated reaction to penicillin, rising to 80 % of patients after 10 years [23].

With regard to the timing of PAP, some authors recommend awake administration prior to induction of anaesthesia as hypotension induced by anaphylaxis can be exacerbated by both general or neuraxial anaesthesia and the severity of physiological changes may be blunted in conscious patients [6]. Furthermore, it may be easier to identify the trigger substance if fewer substances are administered in short succession. The ASA does not recommend this approach, however, and instead recommends securing the airway prior to administration of antibiotics as this course of action reduces the risk of a difficult airway should anaphylaxis occur [13].

Uncommon triggers

Worldwide, **latex** is still a common trigger for POH, although the use of powder-free latex products and increasing avoidance of latex in surgical environments has resulted in a decreasing trend over the past years [3]. Risk factors for latex allergy include diseases and syndromes which are associated with a **high frequency of surgery or interventions**, especially in **childhood** (e.g. spina bifida, oesophageal atresia, etc.). The most significant association is with gynaecological, abdominal and orthopaedic surgery. **Atopy** is also known to be a proven risk factor for latex allergy. In these cases **cross-reactivity with exotic fruits** (avocado, banana, passion fruit, kiwi) is common. Such reactions can be elicited from patient history and may serve as a warning of latex allergy. **Occupational exposure** to latex is also a risk factor for latex allergy [27]. As the **route of exposure is typically dermal or mucosal,** POH triggered by latex typically occurs with a certain **latency** during the steady state of anaesthesia.

The prevalence of **disinfectants** (including chlorhexidine) triggering POH has increased noticeably over the past years [3]. It is worthy of note that disinfectants are used as lubricants, e.g. for insertion of urinary catheters, and as antimicrobial coating on central venous catheters [7]. The initial reaction is typically mild, so that POH may be overlooked [13].

Local anaesthetics, opioids and benzodiazepines very seldom trigger POH [19].

Use of propofol in patients with food allergies?

Propofol is formulated in a lipid solution containing **soybean oil, glycerol and egg lecithin.** Egg, soy and peanut allergies are amongst the most common food allergies in children, and the package insert for propofol warns of its use in patients with allergies against any component of the solution. However, the **soybean oil** contained in propofol emulsion is highly refined, and therefore unlikely to contain a significant level of allergenic particles [28]. The majority of patients with **egg allergy** are allergic to **egg white proteins** [3]. In the less common case of **egg yolk allergy** the allergen is **chicken albumin.** In contrast, propofol contains the phosphatide egg lecithin [27,29]. Whilst purified lecithin can contain traces of egg yolk proteins, the quantity is minute. **Peanut allergy** is listed as a contraindication for propofol use in the package insert due to the potential for cross-reactivity with soy.

Only a handful of case reports of **propofol anaphylaxis** have been published. None of those patients affected were allergic to egg or soy, and the assumption is that the allergen was either the isopropyl group or phenol ring [27].

In conclusion, there is currently no evidence for avoiding propofol in patients with egg, soy or peanut allergies [6, 28, 29].

Treating POH

Early recognition and with that immediate initiation of suitable treatment is decisive for a positive outcome following POH.

Those measure include

- immediately **stopping the administration of the (suspected) trigger** and
- early involvement of **additional personnel.**

Vital functions should be secured in line with the ABCDE approach. Large-bore intravenous access (>18 G for adults) should be established [5]. The decision to place an **intra-arterial line** should be taken liberally.

Early epinephrine administration and adequate volume resuscitation are the two mainstays of pharmacological treatment for POH (Tab. 3) [3,13,14].

Balanced crystalloid solutions should be preferred for volume resuscitation, starting with a bolus of 10–20 ml/kg body weight [5]. When the response is inadequate a repeat bolus may be administered. Further volume resuscitation should be tailored to the severity of POH and – in severe cases – be managed with the aid of extended haemodynamic monitoring (e.g. pulse contour analysis systems) to gauge the volume response.

Table 3
Acute treatment for POH (modified based on [9]).

Grade of hypersensitivity reaction	Presentation	Treatment
Grade III (anaphylaxis) Life-threatening reaction involving multiple organ systems	Severe hypotension +/- tachycardia or bradycardia Severe bronchospasm Pronounced gastrointestinal symptoms Urticaria, flush, angioedema	**Epinephrine** 50–100 µg i.v., if no response double or continuous infusion **Volume resuscitation:** 1 l crystalloid i.v. Consider vasopressin for refractory hypotension persisting >10 min. For β-blocker use: glucagon 1 mg slow i.v. push Antihistamines and glucocorticoids: only following initial stabilisation Begin CPR if RR_{syst} <50 mmHg or $etCO_2$ <20 mmHg
Grade IV (anaphylaxis)	Cardiorespiratory arrest	CPR in accordance with guidelines Epinephrine 1 mg

CPR: cardiopulmonary resuscitation; **$etCO_2$:** end-tidal partial pressure of carbon dioxide; **RR_{syst}:** systolic blood pressure.

Epinephrine, with its effect on both α- and β-adrenergic receptors, is of outstanding importance in the treatment of higher grade POH [16]. It leads to vasoconstriction and reduces capillary permeability and with that the development of oedema; its positive inotropic effect contributes to haemodynamic stabilisation. Furthermore, epinephrine causes bronchodilation and reduces further mediator liberation via a mast cell stabilising effect [16,30]. The 2021 German Dermatological Society S2k guidelines "Anaphylaxis" recommend intramuscular administration as the primary route of epinephrine use outside of cardiopulmonary resuscitation for its depot effect and lesser risk of severe cardiac side effects [14]. Those responsible for the guidelines do point out, however, that this recommendation primarily refers to situations without established intravenous access and add that for patients in shock and on intensive care units the intravenous route should be preferred. The author of this paper is of the opinion that the perioperative setting, in which intravenous access is typically already established, is comparable. Additional intramuscular administration may be considered for the depot effect [5]. The dose should be titrated to effect, using continuous intravenous administration if required.

Antihistamines and glucocorticoids are further pharmacological options for the treatment of POH. The evidence for both substance groups is low. A 2007 Cochrane Review was unable to find any evidence for or against the use of H1-antihistamines for anaphylaxis [31]. For mild hypersensitivity reactions H1-antihistamines may reduce histamine-mediated symptoms as urticaria and pruritus, whilst H2-antihistamines are without effect. As such, H1-antihistamines can be used following stabilisation of vital functions [14].

Epinephrine administration should never be delayed for administration of antihistamines!

The rationale for glucocorticoid use for treatment of anaphylaxis is based on their efficacy in long-term treatment of allergic asthma [16]. A 2012 Cochrane Review was unable to find any randomised, controlled trials examining glucocorticoid efficacy in the acute treatment of anaphylaxis [32]. This situation remains unchanged. Glucocorticoids exert their effects via unspecific membrane stabilising processes in the late phase of anaphylaxis (after 4–6 hours), with a positive effect especially on pulmonary symptoms. Patients displaying pulmonary symptoms may therefore benefit from glucocorticoids, which don't, however, have any place in the emergency treatment of anaphylaxis [2].

In special cases, further reserve drugs may be used. In epinephrine-refractory hypotension persisting over more than 10 minutes, use of norepinephrine and/or vasopressin may be considered. Treatment with glucagon may be attempted in refractory hypotension in patients treated with β-blockers, although it is worth noting that the positive inotropic effect and increased number of β-receptors on the cell surface facilitated by glucagon only address the cardiac symptoms of anaphylaxis [5].

Initiation of cardiopulmonary resuscitation (or chest compressions) is recommended in literature when the invasively determined arterial blood pressure drops below 50 mmHg; current data show this value correlates with pulseless electric activity with a positive predictive value of 90 %, whilst invasive blood pressure measurements also often overestimate the actual blood pressure [16].

Proceeding after POH

The decision to undertake or abort surgery following POH should be taken on the basis of individual patient-related and surgical factors. Comorbidities, the type and severity of the reaction and the response to treatment should be individually weighed against the urgency of the surgical intervention. The predominant recommendation found in literature is to postpone surgery following life-threatening POH unless there is a compelling reason not to.

Grade III or IV POH generally mandates further treatment on an intensive care unit. The risk of so-called biphasic anaphylaxis is small at <5 % [9].

Step-by-Step Diagnostic Approach

Typical signs and symptoms coupled with suspected anaphylaxis should result in perioperative determination of serum mast cell tryptase.

This is a serine protease which is released during immediate-type hypersensitivity reactions, and which can be used as a marker for mast cell degranulation [11,33]. Non-immunologically mediated mast cell activation can also lead to an increase in mast cell tryptase, however, and a lack of increased serum tryptase does not exclude anaphylaxis [7]. Differing statements regarding the timing of testing can be found across literature. Summarising, mast cell tryptase should be determined **within 6 hours of symptom onset** and compared with a basal level at 24–48 hours, as individual baselines vary significantly and some diseases are associated with increased basal levels [3,34]. Tryptase kinetics with an increase in accordance with the internationally developed consensus formula **((1.2 x baseline tryptase) + 2) [µg/ml]** is taken to be evidence of significant mast cell degranulation and is suggestive of anaphylaxis [4,13].

Allergological diagnostics should be undertaken after any and every episode of immediate-type POH [4]. Close cooperation between anaesthesiology and allergology is essential in these cases.

The anaesthesiologist is tasked with providing **detailed descriptions of all drugs and any other substances** used, and a **clear chronology of drug administration** in relation to the development of symptoms [6]. No unequivocal recommendations exist with regard to the timing of allergological follow-up. To avoid false positive or false negative results due to depletion of mediators in mast cells and basophils as well as specific IgE antibodies the majority of authors recommend follow-up **within a timeframe of 4–6 weeks following POH**. These considerations are of a theoretical nature, however; evidence regarding the timing is weak at best [3,6,13].

The aims of allergological diagnostics are to

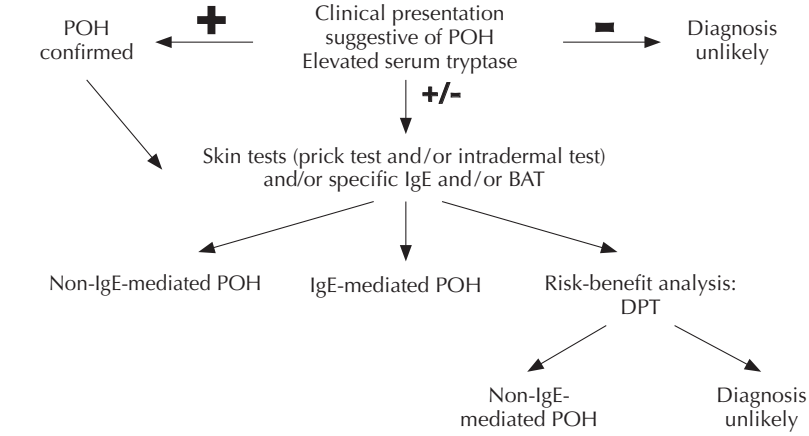
- prove or disprove POH or provide an alternative diagnosis
- identify the mechanism underlying POH (immunological versus non-immunological) and the causative allergen
- in cases of proven IgE-mediated POH with a known trigger (including potential cross-reactivity) determine safe pharmaceutical alternatives
- inform and reassure the patient
- provide recommendations for future anaesthetics [4].

Step-by-step allergological diagnostics include skin tests, in vitro tests (specific IgE, basophil activation test BAT) and provocation tests (drug provocation test DPT). Skin tests (prick test, intradermal test) represent the first stage of allergological evaluation following POH (Fig. 2) [2]. The so-called **prick test** involves applying the potential allergen to the skin, which is then scratched with a lancet. Histamine is used as a positive control, with NaCl used as a negative control. After 15–20 minutes erythema and wheals are evaluated and compared with the positive control. Where the prick test is negative, **intradermal testing**, which is more sensitive but less specific, can follow. **In vitro tests** exhibit relatively low sensitivity and limited availability for the majority of substances used in the perioperative phase [33]. The DPT represents the gold standard for diagnosing both immunological and non-immunological drug reactions [2,24]. Its use in the context of diagnosing POH is limited by the potential risk of severe reactions following parenteral administration and the pharmacological effects of some of the substances to be tested (paralysis, respiratory depression). As such, if DPT is to be undertaken at all, it is limited to centres and there to an intensive care setting [7,13].

In summary, a typical clinical presentation with usually life-threatening signs and symptoms together with increased serum histamine or tryptase concentrations and a positive skin test is proof of an IgE-mediated allergy. Conversely, mild to moderate symptoms together with a negative skin test with or without raised histamine or tryptase levels suggest a non-immunological hypersensitivity reaction.

Where there is reasonable suspicion of POH, an anaesthesia alert card should be issued and later supplemented by an allergy card after an allergological examination [5].

Figure 2



Step-by-step diagnostic approach to POH (modified based on [3]). **POH:** perioperative hypersensitivity reaction; **IgE:** immunoglobulin E; **BAT:** basophil activation test; **DPT:** drug provocation test.

Prevention

A **detailed history of any allergies** should be obtained during **preanaesthesia assessment** of the patient, including the timing and severity of any reaction. **Non-immunological reactions** with generally mild or moderate symptoms are typically triggered by histamine-liberating drugs in young or stressed patients, and those with atopy. The offending drug is **not contraindicated** in these cases. Slow i.v. injection or a reduced dose of the substance in question and **premedication with antihistamines** may reduce or even avoid symptoms [6,27]. In contrast, **immunologically mediated hypersensitivity reactions cannot be suppressed by premedication with antihistamines.** In these cases the trigger and any other substance possibly implemented in cross-reactivity must be avoided [27,35].

Summary

- Perioperative hypersensitivity reactions may be of immunological or non-immunological aetiology. Differentiating between these two aetiologies based on the clinical presentation alone is impossible.
- POH is rare but associated with significant morbidity and mortality.
- Diagnosing POH can be difficult as the signs and symptoms may be masked by the effects of anaesthesia and surgery.
- Antibiotics and neuromuscular blocking agents are amongst the most common triggers of POH.
- A positive outcome following life-threatening anaphylactic reactions is dependent on an early diagnosis and adequate treatment with epinephrine and volume resuscitation.
- Antihistamines and glucocorticoids have no place in the acute treatment of anaphylaxis.
- Patients suffering POH should undergo postoperative allergological follow-up; interdisciplinary cooperation between the anaesthesiologist and allergologist is essential in these cases.

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