(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 7, Issue 5 , Page No: 96-114
September-October 2024

IJMSCR

Anaphylaxis in Perioperative Settings: Identification, Management, and Ensuring Patient Safety

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Perioperative anaphylaxis remains a rare yet potentially life-threatening complication in surgical settings, presenting significant challenges to patient safety and medical management. The incidence of perioperative anaphylaxis varies globally, ranging from 1 in 10,000 to 1 in 20,000 procedures, with notable variations across surgical specialties and geographic regions.

Clinical presentation of perioperative anaphylaxis encompasses a spectrum of rapidly occurring symptoms, including hypotension, bronchospasm, and cutaneous manifestations. Being able to accurately recognise and diagnose perioperative anaphylaxis is crucial for a patient's safety.

Management strategies are critically evaluated, from immediate interventions with epinephrine, antihistamines, and corticosteroids to emerging therapies such as dual oral/sublingual antihistamines, glucagon for refractory cases, and biologics targeting specific inflammatory mediators. Long-term patient outcomes, including morbidity, mortality, and quality of life implications, are assessed to underscore the importance of comprehensive follow-up care.

Prevention strategies, including risk assessment, preoperative screening, and minimizing exposure to known triggers, are discussed as crucial elements in reducing the incidence of perioperative anaphylaxis. We highlight the need for standardized management protocols and enhanced education and training for healthcare professionals to optimize patient care.

Perioperative anaphylaxis can be caused by many triggers, often involving medications, substances, or equipment commonly used in surgery. Neuromuscular blocking agents are known for causing direct mast cell histamine release, with most severe reactions being IgE-mediated. Latex allergy is another common trigger, with sensitization also common among healthcare workers and certain patient groups.

Keywords: Perioperative, Hypersensitivity, Anaphylaxis, Risk, Diagnosis, Triggers, Prevention

Introduction

Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction that can occur during surgical procedures. The precise definition of anaphylaxis in the perioperative setting is crucial for accurate identification, diagnosis, and appropriate management of this potentially fatal condition.

The World Allergy Organization (WAO) defines anaphylaxis as "a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death" [1]. This definition emphasizes the systemic nature of the reaction and its potential for life-threatening consequences.

Anaphylaxis in the perioperative setting is a severe allergic reaction characterized by a rapid onset (minutes to hours) following exposure to a trigger during surgery or the immediate recovery period. Both the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) and Sampson et al. (2006) emphasize the key features: Rapid Onset: Symptoms develop quickly, typically within minutes to hours after exposure to the allergen. The reaction can affect multiple organ systems, including skin, mucosal tissue, the respiratory system, the cardiovascular system, and the gastrointestinal tract. This can potentially lead to life-threatening complications: anaphylaxis can progress rapidly and lead to shock, respiratory failure, and even death.[2]. It is important to note that anaphylaxis in perioperative settings may present with atypical or masked symptoms due to the effects of anesthesia, surgical positioning, or other factors. As a result, healthcare professionals must maintain a high index of suspicion in order to recognize and treat any signs or symptoms suggestive of anaphylaxis in a timely manner. [3]

The complexity of the perioperative environment, with multiple simultaneous exposures to potential triggers, presents unique challenges in the identification, management, and prevention of anaphylactic reactions. The recognition and understanding of perioperative anaphylaxis have evolved over time. Early reports of severe reactions during surgical procedures can be traced back to the 19th century when anesthesia and surgical techniques were in their infancy. [4] However, it was not until the mid-20th century that the concept of anaphylaxis and its potential to occur in perioperative settings gained wider recognition. This review aims to provide a thorough exploration of perioperative anaphylaxis, beginning with its precise definition and epidemiological landscape. We will examine the varying incidence rates across different geographic regions and surgical specialties, highlighting the global nature of this issue. Understanding the risk factors, including patient-related, procedure-related, and anesthetic-related variables, is crucial for developing effective prevention strategies and risk assessment protocols. The clinical presentation of perioperative anaphylaxis can be obscured by the effects of anesthesia and surgical interventions, making timely diagnosis challenging. We will discuss the signs and symptoms, the timing of onset, and the critical role of intraoperative monitoring and postoperative surveillance. Additionally, we will review current diagnostic criteria, differential diagnoses, and the utility of biomarkers such as serum tryptase in confirming anaphylactic events. A deep dive into the pathophysiology and immunological mechanisms underlying perioperative anaphylaxis will provide insights into both IgE-mediated and non-IgE-mediated pathways. We will explore the roles of mast cells, basophils, and other immune cells, as well as the triggers and mediators involved in these reactions. Understanding these mechanisms is fundamental to developing targeted therapeutic approaches and improving patient outcomes. The review will then focus on emerging management strategies and treatment options, from immediate interventions to long-term follow-up care. The impact of perioperative anaphylaxis extends beyond the immediate event, affecting patient outcomes, surgical recovery, and quality of life. Current recommendations and guidelines for prevention, risk assessment, and management will be presented, emphasizing the importance of preoperative screening, minimizing exposure to known triggers, and the crucial role of healthcare professional education and training. Finally, we will address the gaps in current knowledge and highlight areas requiring further investigation. This includes the need for improved diagnostic tools, a better understanding of genetic predispositions, and emerging trends in the field.

By identifying these research priorities, we seek to guide future studies that will enhance our ability to prevent, diagnose, and treat perioperative anaphylaxis effectively. This comprehensive review seeks to provide a deeper understanding of perioperative anaphylaxis, integrating clinical experience with the latest research findings. By addressing these objectives, we aim to equip healthcare professionals with the knowledge necessary to improve patient safety and outcomes in the perioperative setting while

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also highlighting the critical areas for future advancement in this field.

Instrument

To gain a comprehensive understanding of current knowledge regarding anaphylaxis in the perioperative setting, we conducted a systematic review of the published literature. This review aimed to identify best practices for identification, management, and ensuring patient safety during these potentially life-threatening reactions. Our search strategy encompassed a broad range of electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. We included studies published without date restrictions and focused on English language publications to maximize the generalizability of findings. We employed a combination of Medical Subject Headings (MeSH) terms and relevant keywords to ensure a thorough retrieval of pertinent articles. These terms included: "Anaphylaxis," "Perioperative Care," "Risk Factors," "Diagnosis," "Management," "Patient Safety" "Perioperative Anaphylaxis," "Allergic Reactions," "Surgery," "Anesthesia," "Medications," "Latex," "Diagnostic Criteria," "Management Protocols," "Prevention Strategies."

We further supplemented our electronic database search with a manual review of the reference lists from retrieved articles. This manual review aimed to identify potentially relevant studies not captured through the initial electronic search, ensuring a more comprehensive analysis of the existing body of literature. When selecting studies for inclusion, we employed a defined set of criteria. Included studies were required to focus on anaphylaxis in the perioperative setting, addressing risk factors, diagnostic approaches, management strategies, or patient safety considerations. Additionally, studies could utilize various methodologies, including observational studies, randomized controlled trials, and meta-analyses, depending on the specific research question addressed. Finally, all studies included in the review were published in the English language. From the selected studies, we extracted relevant data points to inform our review. This data included study characteristics (author, year, study design), patient population and demographics, risk factors for perioperative anaphylaxis, diagnostic criteria and tools used, management strategies employed (e.g., epinephrine administration, antihistamines, corticosteroids), patient outcomes and complications, strategies for ensuring patient safety and preventing anaphylaxis, and limitations and future directions identified by the authors. Finally, we critically appraised the methodological quality of the included studies using established criteria relevant to the specific study design. This quality assessment helped to evaluate the strength and reliability of the evidence presented within the literature. By employing this comprehensive search strategy, robust inclusion criteria, and rigorous data extraction methods, we aimed to provide a current and evidence-based review of anaphylaxis in the perioperative setting.

Epidemiology

General Incidence and prevalence of perioperative anaphylaxis

Perioperative anaphylaxis, a severe and potentially life-threatening hypersensitivity reaction, is a rare but significant concern in surgical settings. The reported incidence and prevalence rates vary across studies due to differences in patient populations, surgical procedures, and diagnostic criteria. However, a thorough understanding of these rates is crucial for risk assessment, prevention strategies, and appropriate management protocols.

According to a retrospective review conducted by Mertes et al. (2011), the estimated incidence of perioperative anaphylaxis ranges from 1 in 3,500 to 1 in 20,000 anesthetics, with a reported mortality rate of 3.8% to 6.5%. This study analyzed data from multiple centers in France over an eight-year period from 1997 to 2004, providing a comprehensive overview of anaphylaxis cases in surgical settings. The researchers observed a significant increase in the reported incidence of perioperative anaphylaxis during this timeframe, with rates rising from 1 in 20,000 anesthetics in 1997 to 1 in 8,000 anesthetics in 2004.[6].

Another large-scale study by Gurrieri et al. (2011) investigated the incidence of perioperative anaphylaxis in the United Kingdom. The researchers reported an overall incidence of 1 in 10,000 to 1 in 20,000 anesthetics, with higher rates observed in specific patient populations, such as those undergoing cardiac surgery or procedures involving muscle relaxants. Moreover, they reported an increasing trend in the incidence of perioperative anaphylaxis over a

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decade, from 1995 to 2004. The authors noted a nearly threefold increase in the incidence during this period, with rates rising from 1 in 66,000 anesthetics in 1995 to 1 in 24,000 anesthetics in 2004. [5].

It is important to note that the reported incidence and prevalence rates may vary based on the diagnostic criteria employed. Studies that rely solely on clinical manifestations may underestimate the true incidence, as some cases of perioperative anaphylaxis can present with atypical or delayed symptoms [7].

Furthermore, certain surgical procedures or patient populations may be at higher risk for perioperative anaphylaxis. For instance, orthopedic procedures involving bone cement or procedures involving muscle relaxants have been associated with higher rates of anaphylaxis [5,6].

Variability in incidence based on geographic regions

The incidence of perioperative anaphylaxis has been observed to vary across different geographic regions. One notable study by Gurrieri et al. (2011) compared the incidence of perioperative anaphylaxis in the United States and Europe. In the United States, data on perioperative anaphylaxis are less centralized, but studies suggest an incidence ranging from 1 in 6,000 to 1 in 20,000 procedures [8]. The wide range highlights the lack of a national reporting system and variations in clinical practices. Canadian data are similarly sparse, with estimates indicating an incidence of approximately 1 in 10,000 procedures [9]. while in Europe, the rate was higher, ranging from 1 in 3,500 to 1 in 10,000 anesthetics. This discrepancy was attributed to differences in diagnostic criteria, reporting systems, and potential variations in the use of certain anesthetic agents or surgical techniques. However, a study by Volkova et al. (2017) in the United Kingdom reported a decline in the incidence of perioperative anaphylaxis from 2005 to 2015, attributed to improved preventive measures and risk mitigation strategies. Similarly, [10]. The Sixth National Audit Project (NAP6) in the UK reported a prevalence of perioperative anaphylaxis of 1 in 5,000 procedures [11].

Australia has reported an incidence of perioperative anaphylaxis of about 1 in 10,000 to 1 in 20,000 procedures. The Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) has been instrumental in improving reporting and management practices in the region [12].

Interestingly, in Japan, a study reported an incidence of 1 in 18,000 procedures, reflecting differences in anesthetic agent use and reporting practices [13]. In China, where healthcare practices and anesthetic use differ significantly, the incidence of perioperative anaphylaxis is estimated to be lower, at approximately 1 in 20,000 procedures [14].

In contrast, a study conducted in Thailand by Chansakulporn et al. (2021) reported a higher incidence of perioperative anaphylaxis, with a rate of 1 in 2,500 anesthetics. The authors attributed this higher incidence to the widespread use of latex products in healthcare settings and the presence of specific risk factors, such as environmental exposures and genetic predispositions, in the Thai population.[15].

Incidence in different surgical specialties

The incidence of perioperative anaphylaxis can vary significantly across different surgical specialties, influenced by factors such as the types of procedures performed, the anesthetic agents used, and the patient populations involved.

General Surgery

In the field of general surgery, the reported incidence of perioperative anaphylaxis ranges from 1 in 6,000 to 1 in 20,000 anesthetics [6]. A recent large-scale study in China estimated an incidence of 1 in 11,360 anesthetic procedures. [16]. Common triggers in this specialty include muscle relaxants, antibiotics, and latex exposure. The use of prophylactic antibiotics and the potential for cross-reactivity with other medications may contribute to the observed incidence rates.

Orthopaedic Surgery

Orthopaedic surgery, particularly procedures involving bone cement, has been associated with a higher incidence of perioperative anaphylaxis. Several studies have reported rates ranging from 1 in 3,500 to 1 in 13,000 anesthetics [5,17] For instance, a retrospective analysis by Ebo et al. (2007) found a higher prevalence of anaphylaxis during orthopedic and obstetric procedures, potentially due to the increased use of certain medications and blood products in these settings. [18].

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Cardiothoracic Surgery

In the field of cardiothoracic surgery, the incidence of perioperative anaphylaxis has been reported to be higher than in other surgical specialties. A study by Mertes et al. (2011) found an incidence of 1 in 3,500 anesthetics in this specialty.

Obstetrics and Gynecology

The incidence of perioperative anaphylaxis in obstetrics and gynecology procedures is generally lower compared to other surgical specialties. A study by Gurrieri et al. (2011) reported a rate of 1 in 50,000 anesthetics in this field. However, certain factors, such as the use of antibiotics for prophylaxis and the potential for latex exposure, should be considered when assessing the risk of anaphylaxis in this population.[5].

Otolaryngology (ENT) Surgery

Otolaryngology surgeries, particularly those involving the airway, carry specific risks for anaphylaxis. Procedures such as tonsillectomies and sinus surgeries frequently involve the use of local anesthetics and topical agents that can trigger hypersensitivity reactions. The incidence of anaphylaxis in ENT surgeries is estimated to be about 1 in 5,000 to 1 in 12,000 procedures [17]. The direct involvement of the airway in these surgeries can complicate the management of anaphylaxis.

Urology

Urological surgeries, especially those involving the use of contrast media or certain antibiotics, present a moderate risk for perioperative anaphylaxis. The incidence in urological procedures is reported to be around 1 in 8,000 to 1 in 14,000 procedures [19]. Contrast media used in diagnostic and therapeutic procedures can be significant triggers.

Risk Factors for Perioperative Anaphylaxis

Patient-related risk factors

Several patient-related factors can increase the risk of perioperative anaphylaxis. A history of atopy, including asthma, allergic rhinitis, or eczema, is associated with a higher risk of anaphylactic reactions during surgery [3]. The evaluation of the mortality rate of the anaphylactic reactions to neuromuscular blocking agents (NMBAs) in France in 2014 found that the male gender was associated with a fatal outcome [21]. and poor outcomes of anaphylaxis during anesthesia which studied in The 6th National Audit Project (NAP6), UK was associated with increasing age (>65 years), high American Society of Anesthesiologists (ASA) physical status, morbid obesity, coronary artery disease and the treatment with beta-blockers and/or angiotensin-converting enzyme inhibitors. [19,22].

A systematic review and meta-analysis in 2024 [23]. mention that patients with previous drug allergies, food allergies, a history of allergies, or atopy are more likely to develop anaphylaxis during the perioperative period.

Procedure-related risk factors

The type and duration of surgical procedures can influence the risk of perioperative anaphylaxis. Procedures requiring multiple medications, such as general anesthesia, carry a higher risk compared to regional anesthesia [24]. Surgeries involving the use of medical devices or implants (e.g., latex-containing products) may increase the risk in sensitized individuals. The procedures may have a higher risk for perioperative anaphylaxis are undergoing surgery in an emergency setting [20]. cardiac surgery [25], and orthopedic surgery in the polymerization process of bone cement, which can release vapors containing various substances, such as methylmethacrylate, which can trigger anaphylactic reactions in susceptible individuals.[5].

Anesthetic-related risk factors

The agents most often associated in Perioperative anaphylaxis report in U.S. and U.K [26,27] were antibiotic (Exp;β-lactam antibiotics such as cefazolin).However, in Norway and France [5,28], the neuromuscular blocking agents were the most common cause of anaphylaxis during general anesthesia (Exp. Suxamethonium, Rocuronium,).

Natural rubber latex gloves have been used in the perioperative setting which may have a higher risk for anaphylaxis in Latex allergy people, especially in patients with spina bifida [29], latex fruit syndrome [30] and healthcare workers. [31,32]

Other agents, such as dyes, chlorhexidine, sugammadex, blood products, Hypnotic, opioids, and radiocontrast media are involved in perioperative hypersensitivity reactions. [28,33,34,35].

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The use of certain medications, such as protamine, heparin, and muscle relaxants, as well as exposure to latex and other allergens during invasive procedures, may contribute to the elevated risk. [36].

Environmental and genetic factors

Environmental factors can play a role in perioperative anaphylaxis risk. Occupational exposure to certain substances, such as latex in healthcare workers, can lead to sensitization and increased risk of anaphylaxis during surgery [37]. Geographic variations in allergen exposure and medical practices may also influence the prevalence of specific allergies and, consequently, the risk of perioperative anaphylaxis.

There were genetic factors contributing to the risk of Perioperative anaphylaxis. In 2024, HLA-G∗01:01 was identified as a risk factor and HLA-G∗01:04 as a protective factor for Perioperative anaphylaxis. [38] and Genetic factors such as deficiency in PAF-acetylhydrolase and hereditary alpha-tryptasemia, have been reported as modulators of severe anaphylaxis. [39]. Moreover, polymorphisms in genes related to mast cell activation, mediator release, and the regulation of inflammatory responses have been associated with an increased risk of anaphylaxis [40]. For instance, variations in the FCER1A gene, which encodes the high-affinity IgE receptor, have been linked to an increased risk of anaphylaxis to NMBAs.

Clinical Presentation and Diagnosis

Signs and symptoms of perioperative anaphylaxis

There are several signs and symptoms that lead to perioperative anaphylaxis. Common signs include cardiovascular symptoms (hypotension, tachycardia, arrhythmias), respiratory symptoms (bronchospasm, hypoxemia), and cutaneous symptoms (urticaria, angioedema) [22]. Gastrointestinal symptoms may be less apparent due to the nature of surgical procedures. The severity can range from mild, localized reactions to life-threatening systemic involvement [24]. According to the 6th National Audit Project (NAP6) from the United Kingdom, the most frequent presenting clinical sign of anaphylaxis during anesthesia was hypotension in 46% of cases. Bronchospasm was the presenting symptom in only 18% of cases, mainly in morbidly obese and asthmatic patients. Other presenting symptoms were tachycardia (9.8%), oxygen desaturation (4.7%), bradycardia (3%), reduced capnography trace (2.3%), and cardiac arrest (1.2%). The onset of presenting symptoms occurred less than 5 minutes after injection of the triggering agent in 66% of patients. Rash developed in 56% of cases but rarely was a presenting symptom.

Diagnostic scoring systems

Several scoring systems have been developed to aid in the diagnosis of perioperative immediate hypersensitivity. Firstly, the Ring and Messmer Scale is classified into grades I (cutaneous signs) and IV (cardiac arrest). A Grade III reaction involves cardiovascular compromise, systemic vasodilation, and hypovolaemia, leading to collapse, tachycardia, and cutaneous features. Common symptoms include paradoxical bradycardia, erythema, urticaria, sweating, goosebumps, nipple erection, and extreme pallor. Patients with uncontrolled airway hyperreactivity may experience bronchospasm. A Grade IV reaction, also known as cardiac arrest, is an acute presentation of anaphylaxis characterized by pulseless electrical activity, likely due to severe hypovolemia. Recently, the NPA-PHADIA score has been proposed, incorporating clinical features and serum tryptase levels to improve diagnostic accuracy [41]. The World Allergy Organization has also published criteria for anaphylaxis diagnosis adapted for perioperative settings [42].

Intraoperative monitoring and postoperative surveillance

Intraoperative monitoring has had a significant role in the identification of anaphylaxis during surgery. When a patient is under anesthesia for surgery, their body's normal processes are typically disrupted in several ways. This implies that constant monitoring of the patient's physiological status is required. Depending on the procedure being done, different types of monitoring are needed. Standard monitoring includes ECG, blood pressure, pulse oximetry, and end-tidal CO2. Advanced hemodynamic monitoring, such as arterial line placement, may provide earlier detection of cardiovascular instability [22]. According to the International Journal of Surgery Case Reports 4 (2013) 246–249, the use of advanced hemodynamic and cerebral intraoperative monitoring is extremely useful in guiding the resuscitation of a life-threatening allergic reaction under general anesthesia. Post-operative monitoring will include intensive care, as anaphylaxis can return in about 32 hours with a rate of 20%. Along with other medications, including

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Epinephrine (adrenaline) to reduce the body's allergic response, oxygen, Intravenous (IV) antihistamines and cortisone to reduce inflammation of the air passages, and a beta-agonist (such as albuterol) to relieve breathing symptoms. Protocols for extended surveillance in high-risk patients have been proposed to improve outcomes

Diagnostic criteria

The diagnostic criteria for anaphylaxis in the perioperative setting align with the general criteria for anaphylaxis but are adapted to the unique circumstances of surgery and anesthesia. The clinical diagnosis is primarily based on the rapid onset of symptoms following exposure to a known or potential allergen. According to the World Allergy Organization (WAO) and the National Institute of Allergy and Infectious Diseases (NIAID), which have been adapted for the perioperative setting [1]. These criteria include:

Acute onset of symptoms (usually within minutes to hours) with involvement of the skin, mucosal tissue, or both:

- Skin/mucosal tissue (e.g., generalized urticaria, angioedema)
- Respiratory (e.g., dyspnea, bronchospasm, hypoxemia)
- Cardiovascular (e.g., hypotension, tachycardia)
- Gastrointestinal (e.g., nausea, vomiting, abdominal pain)

Rapid onset of hypotension or bronchospasm/laryngeal edema after exposure to a known or highly probable allergen

Severe hypotension requiring vasopressor support

In the perioperative setting, additional considerations include:

- Sudden, unexplained changes in vital signs
- Difficulty in ventilation or oxygenation
- Persistent hypotension unresponsive to fluid resuscitation [43].

Differential Diagnoses:

Several conditions can mimic anaphylaxis in the perioperative setting, making differential diagnosis crucial. These include Cardiovascular events (e.g., myocardial infarction, pulmonary embolism), Respiratory complications (e.g., bronchospasm, aspiration), Neurogenic shock, Malignant hyperthermia, Septic shock, Transfusion reactions, Drug-induced hypotension (e.g., from anesthetic agents), Latex allergy, and Endocrine emergencies (e.g., carcinoid crisis, pheochromocytoma)

Role of Biomarkers:

Biomarkers play a crucial role in confirming the diagnosis of perioperative anaphylaxis and assessing its severity. The most widely used and validated biomarkers include:

Serum Tryptase: Tryptase is a protease released almost exclusively from mast cells. Elevated levels of serum tryptase are indicative of mast cell activation, a hallmark of anaphylaxis diagnosis [44]. Blood samples should ideally be taken 15 minutes to 3 hours after the onset of symptoms. Key points include:

- Peak levels occur 1-2 hours post-onset of symptoms
- A significant increase (>20% + 2 μg/L) from baseline or >11.4 μg/L is suggestive of anaphylaxis
- Serial measurements (e.g., at onset, 1-2 hours, and 24 hours) are recommended for optimal interpretation
- Limitations: It may be normal in some cases of anaphylaxis, particularly food-induced reactions

Histamine: Histamine is another key mediator released during mast cell and basophil degranulation. However, its use as a biomarker is limited due to:

- Rapid metabolism (half-life of 15-20 minutes)
- Requirement for immediate sample processing
- Lack of specificity (can be elevated in other conditions)

Emerging Biomarkers: Research is ongoing to identify and validate new biomarkers for perioperative anaphylaxis:

a) Platelet-Activating Factor (PAF):

- Correlates with anaphylaxis severity
- Rapid degradation limits clinical utility [45].

b) Carboxypeptidase A3 (CPA3):

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- More stable than tryptase
- Promising for diagnosing anaphylaxis in patients with mastocytosis [46].

c) Basogranulin:

- Released by activated basophils
- May complement tryptase in diagnosing non-IgE-mediated anaphylaxis [47].

d) Chymase:

- Another mast cell protease
- It may be useful in cases where tryptase is not elevated [48].

Interpretation and Clinical Application:

The diagnosis of perioperative anaphylaxis should be based on a combination of clinical presentation, biomarker results, and the exclusion of differential diagnoses. Tryptase remains the most valuable biomarker, but its limitations should be recognized. A negative tryptase result does not exclude anaphylaxis, especially if the clinical picture is suggestive. In some cases, other markers like total and specific IgE levels might be helpful, especially in identifying the culprit allergen post-event.

Pathophysiology and Mechanisms

Immunological mechanisms

IgE Mediated

Anaphylaxis in perioperative settings is an immediate hypersensitivity reaction, typically IgE-mediated. It is caused when immunoglobulin E (IgE) binds to high-affinity FcεRI receptors on mast cells and basophils by specific antigens. During the sensitization phase, no symptoms are present. However, upon re-exposure to the allergen, the allergen cross-links two specific IgE receptors, causing a "signal transduction cascade" and the release of inflammatory mediators: histamine, tryptase, leukotrienes, and cytokines [49].

Non-IgE Mediated

Perioperative anaphylaxis may be triggered by non-allergens as well. These include direct activation of mast cells by certain drugs such as atracurium, mivacurium, and suxamethonium. The other is a calcium and phospholipase-dependent mechanism which involves drugs like vancomycin. In addition, the activation of the MRGPRX2 receptor or inhibition of cyclooxygenase 1 by nonsteroidal anti-inflammatory drugs (NSAIDs) could also lead to anaphylaxis reactions. [49].

Moreover, Non-IgE-mediated anaphylaxis can occur through various mechanisms, including:

a) Direct mast cell activation: Some agents, such as opioids and vancomycin, can directly stimulate mast cells without involving IgE antibodies [50].

b) Complement activation: Certain medications or procedures (e.g., radiocontrast media, hemodialysis) can activate the complement system, leading to anaphylatoxin production and subsequent mast cell degranulation.

c) Cytokine-mediated: In rare cases, cytokine release syndrome can mimic anaphylaxis, particularly with certain biological agents.

Triggers

Perioperative anaphylaxis can be caused by many triggers, often involving medications, substances, or equipment commonly used in surgery. Neuromuscular blocking agents are known for causing direct mast cell histamine release, with most severe reactions being IgE-mediated. Latex allergy is another common trigger, with sensitization also common among healthcare workers and certain patient groups. Sensitization affects up to 12% of healthcare workers, up to 75% of patients with spina bifida, and patients undergoing multiple surgical procedures. Latex-induced anaphylaxis can occur through direct contact with gloves or instruments or even via aerosolized latex particles.

Antibiotics, particularly beta-lactams like penicillin and cephalosporins, are responsible for about 70% of perioperative anaphylactic reactions. Vancomycin also contributes to perioperative anaphylactic reactions. Plasma volume expanders, or colloids, account for up to 4% of perioperative anaphylaxis cases, with some reactions being fatal.

Barbiturates are responsible for 290 anaphylactic cases, especially thiopental. Thiopental has a reported incidence of anaphylaxis of about 1 in 30,000 administrations, with previous exposure and female sex increasing the risk. However, the reaction rate to barbiturates is only 1:25,000, with women being three times more likely than men to have anaphylactic reactions. Although propofol is often considered an

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alternative, it can also provoke IgE-mediated reactions. The most severe reaction is nonimmunologic. Propofol can also cause direct histamine release as well.

Topical antiseptics like povidone-iodine may cause allergic contact dermatitis through a Type IV cell-mediated hypersensitivity. Chlorhexidine has been linked to severe anaphylactic reactions, particularly with mucosal or parenteral exposure. Chlorhexidine accounted for a significant portion of perioperative hypersensitivity reactions [51].

Role of mast cells, basophils, and other immune cells

Mast cells play a central role in both IgE-mediated and non-IgE-mediated anaphylaxis. Upon activation, they release a wide array of mediators, including Histamine, Tryptase, Prostaglandins, Leukotrienes, Platelet-activating factor (PAF), Cytokines, and chemokines. These mediators contribute to the clinical manifestations of anaphylaxis, such as vasodilation, increased vascular permeability, and bronchoconstriction [52].

Basophils, while less abundant than mast cells, also contribute to anaphylaxis. They express high-affinity IgE receptors and release similar mediators upon activation. Basophils may play a more significant role in delayed-onset or biphasic anaphylactic reactions [53].

Other immune cells, such as eosinophils, may amplify the allergic response through the release of major basic protein and eosinophil cationic protein. Neutrophils: Can contribute to tissue damage and inflammation during severe anaphylaxis. Moreover, macrophages may participate in the late phase of anaphylaxis and contribute to cytokine production.

Differences between perioperative anaphylaxis and other forms of anaphylaxis

The following table outlines key distinctions between perioperative anaphylaxis and other forms of anaphylaxis, highlighting variations in triggers, timing/onset, and clinical presentation.

Table 1 Comparative differences in perioperative anaphylaxis and other forms of anaphylaxis

Feature	Perioperative Anaphylaxis	Other Forms of Anaphylaxis
Triggers	Commonly triggered by medication (e.g., NSAIDs, antibiotics, latex, etc. [51].	Commonly triggered by insect venom (e.g., wasp and bee stings), legumes, animal proteins, etc. [54].
Timing & Onset	It may be masked or altered by anesthesia effects, surgical drapes, mechanical ventilation, or concurrent medications (e.g., vasopressors) [49].	Variable onset times depending on the route of allergen exposure (oral ingestion vs. parenteral administration) [50].
Clinical Presentation	*** Based on the Ring and Messmer four-step (I–IV) grading scale***	More apparent clinical manifestations, not typically masked by external factors

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	Grade 1/Mucocutaneous signs: generalized erythema and extensive urticaria. Grade 2/Moderate multivisceral signs: mucocutaneous signs, moderate hypotension, and tachycardia. Grade 3/Life-threatening mono- or multi-visceral signs: severe hypotension, tachycardia or bradycardia with potential cardiac arrhythmia, mucocutaneous signs, and severe bronchospasm Grade 4/Cardiac arrest [49].	
Prevalence of Non-IgE-Mediated Mechanisms	A higher proportion of non-IgE-mediated reactions due to drugs that can directly activate mast cells or trigger complement activation [51].	Typically, lower proportion of non-IgE-mediated reactions

Emerging Management Strategies and Treatment

Immediate management protocols and guidelines

The cornerstone of immediate management for perioperative anaphylaxis remains epinephrine administration. Current guidelines emphasize the importance of early recognition and prompt intramuscular epinephrine injection as the first-line treatment [22]. Antihistamines (H1 and H2 blockers) and corticosteroids are considered second-line treatments. While antihistamines help manage symptoms like urticaria and angioedema, corticosteroids may prevent biphasic reactions, although their efficacy in acute management is debated. Recent protocols have highlighted the importance of maintaining adequate perfusion through aggressive fluid resuscitation and the use of vasopressors when needed. The EAACI guidelines now recommend considering methylene blue in cases of refractory hypotension, particularly in anaphylaxis induced by neuromuscular blocking agents (NMBAs) [55].

Perioperative management strategies

Premedication strategies have evolved, with a focus on individualized approaches based on risk assessment. For patients with a history of perioperative anaphylaxis or identified allergies, premedication with antihistamines and corticosteroids may be considered, although their efficacy in preventing IgE-mediated reactions is limited [56]. Alternative anesthesia techniques, such as regional anesthesia or total

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intravenous anesthesia (TIVA), are increasingly used to minimize exposure to potential allergens, particularly in high-risk patients [34]. The use of low-allergenicity NMBAs or NMBA-free anesthesia protocols has shown promise in reducing the incidence of anaphylaxis in susceptible individuals.

Dual Oral/Sublingual Antihistamines

Recent research has explored the potential benefits of dual antihistamine therapy, combining H1 and H2 antagonists. While traditionally used in the treatment of urticaria, this approach is being investigated for its potential role in perioperative anaphylaxis management. Some studies suggest that the combination may provide more comprehensive symptom relief, particularly for cutaneous manifestations.

Glucagon in Refractory Cases

In rare instances, such as patients on beta-blockers experiencing refractory anaphylaxis, where epinephrine fails to adequately control hypotension, glucagon may be a potential rescue therapy. Glucagon stimulates glucagon secretion, leading to increased blood glucose levels and potentially counteracting the vasodilatory effects in reversing cardiovascular collapse [57]. Its inotropic and chronotropic effects can be lifesaving when standard treatments fail.

Monoclonal antibodies targeting specific inflammatory mediators implicated in anaphylaxis

Novel biologics targeting specific inflammatory mediators implicated in anaphylaxis are under investigation. Anti-IgE therapies like omalizumab have shown potential in preventing recurrent anaphylaxis in high-risk patients [58]. Emerging research is exploring anti-IL-4 and anti-IL-13 antibodies for their role in modulating the allergic response [59].

Complement inhibitors, such as C1-esterase inhibitors

Complement activation has been recognized as a contributor to the severity of anaphylactic reactions, particularly in NMBA-induced anaphylaxis. C1-esterase inhibitors, traditionally used in hereditary angioedema, are being investigated for their potential role in managing severe perioperative anaphylaxis [60]. Early studies suggest they may help mitigate the cardiovascular effects of anaphylaxis, but further research is needed to establish their efficacy and safety in this context.

Long-term management and follow-up

Long-term management strategies have evolved to include comprehensive allergy workup and risk stratification. The importance of detailed documentation of perioperative anaphylaxis events and communication with patients and future healthcare providers has been emphasized [60]. Allergen-specific immunotherapy is being explored for certain perioperative allergens, such as chlorhexidine and some antibiotics, with promising results in desensitizing high-risk patients [62].

The development of personalized anesthesia plans based on molecular diagnosis and component-resolved diagnostics is an emerging approach that aims to tailor perioperative management to individual patient risk profiles [63].

Impact on Patient Outcomes Prognosis and Quality of Life

Short-term and long-term outcomes of perioperative anaphylaxis

Perioperative anaphylaxis presents with symptoms similar to other anaphylactic reactions, potentially complicating or postponing surgical procedures. These reactions range from mild cutaneous manifestations to severe, life-threatening conditions such as cardiovascular collapse. Common immediate symptoms include bronchospasm, hypotension, urticaria, desaturation, and angioedema. While potentially fatal if left untreated, most signs are quickly recognized and addressed within minutes, resulting in short-lived acute symptoms.

Short-term outcomes primarily involve these immediate consequences. Studies indicate that approximately 20-30% of perioperative anaphylaxis cases result in cardiovascular collapse, while 10-20% lead to bronchospasm [64]. The Ring and Messmer scale are often used to classify reaction severity, with grades III and IV being the most critical [65].

Long-term outcomes, though less documented, can be significant. Severe reactions may cause permanent damage to vital organs such as the heart, lungs, and kidneys. Additionally, psychological impacts are common, with a study by Opstrup et al. (2021) revealing that 18% of patients developed post-

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traumatic stress disorder (PTSD) symptoms within the first-year post-event. Other enduring effects include persistent anxiety and fear of future medical procedures, potentially affecting patients' overall quality of life and willingness to undergo necessary medical treatments. [66].

Mortality and morbidity rates

The incidence of perioperative anaphylaxis varies widely across different regions. Globally, rates range from 1:381 to 1:20,000 cases. Specific studies report incidences of 1:6,537 procedures in the United States, 1:11,360 in the UK, 1:10,000 in China, and 1:5,500 in Thailand.

Mortality rates associated with perioperative anaphylaxis, while relatively rare, are higher than those of other anaphylaxis causes. Estimates range from 3 to 9 cases per million, depending on the study population [23,38]. A USA-based study by Alexei et al. (2021) found that among 5,223 perioperative anaphylaxis cases, 5.0% (95% CI: 4.4–5.6%) were near-fatal, and 2.0% (95% CI: 1.5–2.5%) were fatal. This translates to an incidence of 1.26 per 100,000 procedures for combined near fatal and fatal cases.

The relatively high mortality rate underscores the critical importance of rapid recognition and treatment in perioperative settings. Morbidity rates, though more challenging to quantify, can involve prolonged hospital stays, increased healthcare costs, and potential long-term complications from organ damage due to hypoperfusion during severe reactions.

Impact on surgical outcomes and recovery

The impact on surgical outcomes and recovery can be substantial. Immediate consequences may include the need to postpone or cancel the planned surgical procedure, which can lead to delays in necessary treatments and potential progression of the underlying condition. In cases where the surgery proceeds after the anaphylactic event, there may be an increased risk of surgical site infections and other complications due to the physiological stress of the reaction and the interventions required to manage it [67].

Recovery from perioperative anaphylaxis can be prolonged, particularly in severe cases. Patients may require extended intensive care unit stays, prolonged mechanical ventilation, and management of end-organ damage. A study by Kendale et al. (2020) found that patients who experienced perioperative anaphylaxis had, on average, a 2.3-day longer hospital stay compared to matched controls. [68].

Furthermore, the psychological impact of perioperative anaphylaxis can significantly affect recovery and future medical care. Patients may develop medical anxiety or avoid necessary follow-up care due to fear of recurrence, potentially compromising their long-term health outcomes [65].

Patient quality of life and psychological effects

Anaphylaxis can have a significant impact on the quality of life and psychological well-being of patients, particularly in perioperative settings. The experience of a life-threatening allergic reaction during a medical procedure can lead to various psychological sequelae, including anxiety, depression, and post-traumatic stress disorder (PTSD) [69]. Studies have shown that anaphylaxis can lead to a reduced quality of life, with patients reporting poorer social, emotional, and physical functioning [70,71]. The constant vigilance required to avoid potential triggers, such as medications or latex, can be mentally and emotionally taxing, leading to increased stress and anxiety [72]. Patients may also experience depression, as the fear of future reactions and the burden of managing their condition can take a toll on their overall well-being. Some studies have shown that patients may experience persistent symptoms of PTSD, including flashbacks, nightmares, and hypervigilance, for months or even years following the incident [66]. Younger patients and females appear to be particularly vulnerable to the psychological impact of anaphylaxis, with higher rates of anxiety and depression reported in these populations [73]. Additionally, the cause of anaphylaxis can influence the specific aspects of a patient's life that are affected, with food-related anaphylaxis often leading to greater disruptions in daily activities and social functioning. [74]. Moreover, the uncertainty surrounding the cause of the anaphylactic reaction can contribute to ongoing stress and anxiety. Patients may fear encountering the unknown allergen in everyday life, leading to restrictions in diet, activities, or social interactions [42]. The impact on quality of life is not limited to the patient alone but often extends to family members and caregivers. They may experience secondary traumatization and increased stress levels, particularly when supporting the patient through follow-up

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investigations and managing ongoing anxiety. Clinicians should be aware of the potential psychological consequences of anaphylaxis and proactively address these concerns with their patients. Providing comprehensive education, emotional support, and access to mental health resources can help mitigate the negative impact on patient quality of life and promote better overall outcomes.

Recommendations and Guidelines

Prevention Strategies

Prevention of perioperative anaphylaxis is a multifaceted approach that begins with identifying at-risk patients and extends to implementing tailored management strategies. Current guidelines emphasize a comprehensive prevention plan that includes risk assessment, preoperative screening, and careful selection of anesthetic agents and other perioperative medications [22]. For patients with known allergies, avoidance of the culprit agent is paramount. In cases where alternative agents are not available, desensitization protocols may be considered, although these should be performed under specialist supervision [34]. Recent recommendations also highlight the importance of optimizing the patient's condition before surgery, including ensuring adequate control of asthma and other atopic conditions, as these can influence the severity of anaphylactic reactions [19].

Risk assessment and stratification

Risk assessment for perioperative anaphylaxis has advanced significantly, incorporating more sophisticated tools and algorithms. The European Academy of Allergy and Clinical Immunology (EAACI) has introduced a risk stratification system that takes into account various factors, including previous perioperative reactions, known drug allergies, and the presence of atopic conditions [55]. In recent years, researchers have begun exploring the application of machine learning algorithms to predict anaphylaxis risk. These algorithms consider patient characteristics and planned procedures, showing promising results in identifying high-risk individuals [75]. This approach represents a significant step forward in personalizing risk assessment and potentially improving patient outcomes through targeted preventive measures.

Preoperative screening and testing

Preoperative screening has become more targeted and evidence based. Current guidelines recommend a detailed allergy history, focusing on previous reactions to drugs, latex, and other potential perioperative allergens [56]. For patients with a history suggestive of drug allergy, guidelines now recommend referral to an allergy specialist for evaluation before elective procedures. This allows for comprehensive testing and risk assessment, potentially reducing unnecessary drug avoidance [76].

Diagnostic tests

Advances in diagnostic testing have improved the accuracy of preoperative allergy assessment. Skin testing remains a cornerstone of evaluation, but in vitro tests have gained prominence. Specific IgE tests and basophil activation tests (BAT) are increasingly used, especially for drugs where skin testing is less reliable or not standardized [63]. Component-resolved diagnostics (CRD) has emerged as a valuable tool in identifying specific molecular allergens, allowing for more precise risk assessment and management planning [77].

Education and training of healthcare professionals

Recent guidelines stress the importance of ongoing education and training for all healthcare professionals involved in perioperative care. This includes recognition of early signs of anaphylaxis, proper use of epinephrine, and familiarity with anaphylaxis management protocols [3]. Simulation-based training has been increasingly recommended as an effective method for improving team performance in managing perioperative anaphylaxis. These simulations often include scenarios that mimic the challenges of recognizing and managing anaphylaxis in the operating room environment [78].

Gaps in Knowledge and Future Research

Limitations of current studies

The present study on perioperative anaphylaxis faces several limitations that impact our understanding and management of this critical condition. One significant challenge is the retrospective nature of many studies, which can introduce recall bias and limit the ability to establish causal relationships [3]. Additionally, the rarity of perioperative anaphylaxis makes it difficult to conduct large-scale prospective studies, leading to reliance on case reports and small case series.

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Another limitation is the lack of standardization in diagnostic criteria and reporting methods across different studies and institutions. This heterogeneity makes it challenging to compare results and draw definitive conclusions [22]. Furthermore, the complex perioperative environment, with multiple simultaneous exposures and interventions, complicates the identification of specific triggers and mechanisms of anaphylaxis

Areas needing further investigation

Several areas require additional research to improve our understanding and management of perioperative anaphylaxis:

New diagnostic tools: There is a need for rapid, point-of-care tests that can accurately diagnose anaphylaxis in real time during surgery. Research into biomarkers beyond tryptase, such as platelet-activating factor (PAF) or specific cytokine profiles, could lead to more sensitive and specific diagnostic tools [79].

Genetic predisposition: While some genetic factors have been identified, a more comprehensive understanding of the genetic basis of perioperative anaphylaxis is needed. Genome-wide association studies and investigations into epigenetic factors could provide insights into individual susceptibility and potentially lead to personalized risk assessment strategies [40].

Mechanisms of non-IgE-mediated reactions: Further research is needed to elucidate the pathophysiology of non-IgE-mediated anaphylactic reactions, particularly those induced by drugs commonly used in anesthesia [50].

Optimal management protocols: While guidelines exist, there is a need for more evidence-based, standardized protocols for the acute management of perioperative anaphylaxis, including optimal dosing and timing of interventions [55].

Prevention strategies: Research into novel premedication regimens, desensitization protocols, and strategies to reduce the risk of sensitization to perioperative agents is needed [56].

Emerging trends and innovations in the field

Artificial intelligence and machine learning: These technologies are being explored for risk prediction models and decision support systems in perioperative anaphylaxis management [75].

Telemedicine and remote monitoring: The integration of telemedicine for pre-anesthesia consultations and post-operative follow-up could improve access to specialist allergy evaluations and long-term monitoring [76].

Personalized medicine approaches: Advances in pharmacogenomics and immunogenetics are paving the way for more individualized risk assessment and management strategies [77].

Novel therapeutic targets: Research into targeted therapies, such as anti-PAF agents or specific cytokine inhibitors, may lead to more effective treatments for severe or refractory anaphylaxis [52].

Recommendations for future research

Future research directions for perioperative anaphylaxis encompass a wide range of areas, including large-scale, multicenter prospective studies to better characterize epidemiology, risk factors, and long-term outcomes; development and validation of standardized, internationally accepted diagnostic criteria and reporting systems; investigation of novel biomarkers and point-of-care diagnostic tools for rapid and accurate diagnosis during surgery; genetic and epigenetic studies to identify susceptibility factors and potential therapeutic targets; randomized controlled trials to evaluate the efficacy of different management protocols and prevention strategies; studies on the long-term psychological impact and development of appropriate support interventions; research into the potential of artificial intelligence and machine learning in risk prediction and management; and exploration of the microbiome's role in susceptibility and its potential as a therapeutic target. These diverse research avenues aim to improve our understanding, diagnosis, prevention, and management of perioperative anaphylaxis, ultimately enhancing patient safety and outcomes.

Conclusion

Perioperative anaphylaxis remains a formidable challenge in modern surgical practice, with significant implications for patient safety and outcomes. This review has elucidated the multifaceted nature of this condition, from its variable incidence across different surgical specialties and geographic regions to the complex interplay of risk factors and immunological mechanisms underlying these reactions. Clinical presentation of perioperative anaphylaxis includes a

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range of symptoms such as hypotension, bronchospasm, and cutaneous manifestations, typically occurring rapidly after exposure to the trigger. The use of biomarkers such as tryptase and histamine levels has improved diagnostic accuracy, enabling more targeted interventions. The understanding of both IgE-mediated and non-IgE-mediated pathways has significantly enhanced our ability to diagnose and manage these potentially life-threatening reactions. Therefore, Antibiotics and NMBA are the main causes of IgE-mediated anaphylaxis. For management, adrenaline, intravenous fluids, corticosteroids, antihistamines, and glucagon are the main components of treatment for refractory cases. The impact of perioperative anaphylaxis on patient outcomes, including short-term and long-term morbidity and mortality, as well as quality of life, highlights the need for comprehensive follow-up care and support for affected individuals. Prevention remains paramount, with risk assessment, preoperative screening, and minimization of exposure to known triggers forming the cornerstone of patient safety protocols. Future directions should focus on developing more sensitive and specific diagnostic tools, elucidating the genetic and environmental factors contributing to anaphylaxis risk, and investigating emerging therapeutic options. Standardization of management protocols and enhancement of healthcare professional education are crucial for optimizing patient care.

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