# Anaphylaxis

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## Case Study

Joan has a history of asthma and is scheduled for a ventral hernia repair. She requested no preoperative medication and no antibiotics were ordered. Within a minute of receiving a standard induction with propofol, fentanyl, and rocuronium, Joan developed generalized urticarial erythema and became hypotensive. Mask ventilation became exceedingly difficult, and a second practitioner noted bilateral wheezing. The airway was secured with an endotracheal tube, and Joan received epinephrine 10 µg IV, a 2L fluid bolus, and sugammadex 16 mg/kg IV. Within 7 minutes, hemodynamics and peak airway pressure improved. After 10 minutes of observation, the case proceeded without incident. No additional muscle relaxant was given.

What risk factors contributed to this complication? Was Joan managed appropriately? Keep this clinical scenario in mind as we take a deep dive into anaphylaxis that occurs inside the operating room.

## Anaphylaxis: Pathophysiology & Treatment

Anaphylaxis is an immune-mediated reaction that can produce shock and multiorgan failure.

What is the pathophysiology of anaphylaxis? Before a patient can experience an anaphylactic event, she must first be exposed to an antigen or to a substance that produces cross-sensitivity to the antigen. Exposure follows a two-step process. The primary exposure causes B cells to produce antibodies (most commonly IgE) that bind to Fc receptors on the surface of mast cells and basophils. The patient does not exhibit outward signs or symptoms during primary exposure.
Upon secondary exposure, the antigen binds to the IgE antibodies on the surface of mast cells and basophils, where cross-linkage of these antibodies ultimately culminates in cell degranulation. The process of degranulation is characterized by the release of a variety of mediators such as histamine, tryptase, bradykinin, serotonin, platelet activating factor, and products of arachidonic acid metabolism including prostaglandins and leukotrienes. Vascular nitric oxide production increases, cytokine production increases, and the complement pathway becomes activated.

Before we go further, I want to review the difference between anaphylactic and anaphylactoid reactions. As we just learned, anaphylaxis is an immune-mediated reaction that requires sensitization and antibody production. By contrast, an anaphylactoid (or non-immune mediated) reaction does not require previous sensitization and is not mediated by antibodies. Instead, the offending agent itself triggers mediator release from mast cells and basophils. Because the clinical presentation and treatment of both types of reactions are the same, we won't distinguish between anaphylactic and anaphylactoid reactions as we continue our review.

How does anaphylaxis present? Anaphylaxis related to intravenous administration typically presents within 5 minutes, although the response can be delayed as long as 20 minutes or more. Cardiovascular signs include vasodilation with a profound capillary leak that contributes to hypovolemia and hypotension. The heart rate increases (although bradycardia can occur), and inadequate perfusion can result in cardiac dysrhythmias and even cardiac arrest. Bronchoconstriction increases airway resistance that manifests as wheezing, and pulmonary mucus secretion increases. V/Q mismatch contributes to

hypoxemia and an increased $PaCO_2$ to $EtCO_2$ gradient. Dermatologic manifestations include hives (otherwise known as urticaria), flushing, erythema, pruritus, and swelling (which can lead to airway obstruction). GI complications include nausea, vomiting, abdominal cramping, and diarrhea.

Why is anaphylaxis in the operating room difficult to diagnose? An anesthetized patient is unable to report symptoms, and surgical drapes can obscure the telltale dermatologic signs. Therefore, the presentation of anaphylaxis under anesthesia typically involves the non-specific cardiorespiratory signs that remain on the screen. To complicate matters, hypotension can be misattributed to the cardiovascular effects of anesthetic agents, hypovolemia, or histamine release from drugs such as morphine, atracurium, or meperidine.

What is the treatment of anaphylaxis? Treatment is comprised of inhibiting mediator release plus supportive measures. Primary treatment includes the following:

- Stop antigen exposure to prevent further mediator release. For instance, remove the latex Foley catheter or discontinue the antibiotic infusion.
- Manage the airway with 100% oxygen. Be aware that upper airway and laryngeal swelling can complicate airway management.
- Turn off anesthetic agents. Although inhaled anesthetics promote bronchodilation, this benefit is greatly outweighed by vasodilation and myocardial depression.
- Resuscitate with a crystalloid solution. Two to four liters may be required to compensate for the capillary leak.
- Epinephrine is the drug of choice, because it provides 4 key benefits: alpha-1 stimulation causes vasoconstriction, beta-1 stimulation increases inotropy, and beta-2 stimulation promotes bronchodilation and inhibits mediator release from mast cells and basophils. The dose ranges from 5 – 10 mcg IV for hypotension and 0.1 – 1 mg IV for cardiovascular collapse. An infusion of 0.05 – 0.1 mcg/kg/min may be required. Be careful not to give more epinephrine than the clinical picture dictates, as overdose can precipitate ventricular dysrhythmias.

Secondary treatment of anaphylaxis includes the following:

- Administer antihistamines, such as diphenhydramine (0.5 – 1 mg/kg IV) to antagonize the H1 receptor and famotidine (20 mg IV) to antagonize the H2 receptor. While these agents don't reduce histamine release, they do compete against histamine at their respective receptor targets.
- Bronchodilators (such as albuterol) can be used to treat bronchospasm.
- Corticosteroids (such as hydrocortisone 0.25 – 1 g IV) attenuate the inflammatory response. While they don't provide a clear benefit during the acute phase, corticosteroids are given to prevent a late-phase reaction, typically becoming efficacious 4 – 6 hours after administration.
- Sodium bicarbonate (0.5 – 1 mEq/kg IV) is indicated in the setting of acidosis and/or persistent hypotension. Recall, that catecholamines lose efficacy in the setting of an acidic environment, so improving pH restores the effectiveness of life-saving epinephrine.
- Refractory hypotension is corrected with vasopressin (start at 0.01 units/min IV) or norepinephrine (0.05 – 0.1 mcg/kg/min IV).
- The patient on a beta-blocker may be resistant to epinephrine and may benefit from glucagon for inotropic support and ipratropium for bronchodilation.
- Airway edema must be evaluated prior to tracheal extubation. Facial edema suggests airway involvement. A leak test may be performed prior to extubation or the airway may be inspected under direct vision laryngoscopy.

How should you manage the patient following resuscitation? It's imperative that we identify the offending agent, so the patient isn't re-exposed during a future anesthetic. Given that we administer many drugs at the same time and the variable time course of anaphylaxis, it can be difficult to isolate the offending agent while in the operating room. You should monitor the patient for 24 hours, inform the patient of the complication, and refer the patient to an allergist who'll identify the offending agent. This process will most likely include skin testing at least 4 – 6 weeks following the event. Tryptase, a physiologic marker consistent with degranulation, remains elevated for approximately 2 hours following anaphylaxis. A

blood specimen collected during this time will eventually aid in the diagnosis. Plasma histamine is also useful, but given its short half-life (t1/2 = 15 – 20 minutes) it may be difficult to obtain.

## Clinical Concerns

Anaphylaxis is rare with epidemiologic data on its incidence notably poor because reporting is not universally mandated and the clinical definitions associated with severe allergic reactions are somewhat ill-defined. Textbook and authoritative lecturers often cite an incidence of less than 1 in 10,000 to 20,000 anesthetic cases, with a rate of mortality approaching 4%.

What are the most likely causes of anaphylaxis? Outside of the operating room, the most common cause is food allergy, but inside of the operating room, the most common causes (in descending order) include neuromuscular blockers, latex, and antibiotics.

Of note, a recent retrospective investigation highlights that most of what we know about the etiology was obtained from outside the United States, and it goes on to assert that antibiotics are the most common cause of anaphylaxis inside of this country (1). This should be considered in context, however, as the sample only included 38 patients who suffered perioperative anaphylaxis from any cause over an 18-year period.

Other etiologies common to the perioperative environment include NSAIDs, sedative-hypnotics, opioids, protamine, local anesthetics, colloids, radiocontrast dye, bone cement, blood transfusion, and even chlorhexidine or methylene blue (2, 3).

Who is at increased risk of anaphylaxis? Populations at risk include those with asthma, atopy, systemic mastocytosis, hereditary angioedema, or a history of perioperative anaphylaxis (1). Interestingly, some evidence suggests that the patient on a beta blocker or an ACE inhibitor may also be at increased risk, although this data is largely based on case reports and retrospective analysis (2). It could be that these patients are simply more susceptible to hemodynamic compromise should anaphylaxis occur.

Although the use of latex is on the decline, it's worth reviewing that latex allergy is more likely in patients with spina bifida, those who've undergone multiple surgical procedures, health care workers, as well as those allergic to certain foods including banana, kiwi, avocado, papaya, pineapple, chestnut, and buckwheat.

How should we assess our patients? Beyond asking "do you have any allergies?" some argue a need for systematic screening before anesthesia and surgery; however, the implications of this recommendation involve complex logistics and a significant economic outlay. Minimally, a detailed history of drugs and foods that have provoked an allergic reaction, perhaps even extending to genetically related family members, should be performed during every pre-anesthetic workup. In the patient who reports a history of an allergic reaction, we should tailor our pre-operative interview to determine whether or not the patient truly experienced an anaphylactic event, as patients are often unclear about the true nature of their experiences.

Is pretreatment of at-risk patients efficacious? While some practitioners pretreat at-risk patients with antihistamines and corticosteroids, strong evidence that validates this practice is lacking. One exception may be pretreatment in patients who've experienced a previous allergy-like reaction to radiocontrast dye, although some authors assert the risk of harm imposed by corticosteroids outweighs the perceived benefit. (1).

## New Perspectives On Clinical Dogmas

If we examine the more recent, high-quality epidemiological studies good evidence emerges that can help us with clinical decision making in the operating room. We'll address three topics of high clinical value: anaphylaxis related to neuromuscular blockers, giving a "test dose" in the operating room, and administering a cephalosporin in a penicillin-allergic patient.

While any of the neuromuscular blockers can produce anaphylaxis, not all of these drugs are equivalent in this ability. A recent investigation in the United States concluded that succinylcholine and rocuronium should be viewed as the most common causes of muscle relaxant induced anaphylaxis, affecting roughly 1 in 2,000 and 1 in 2,500 patients, respectively. By comparison, the authors noted the incidence with atracurium as 1 in 22,000 (1).

Investigations from France, Denmark, and Norway have also documented a high incidence of muscle relaxant induced anaphylaxis (2, 3). The Norwegian Medicines Agency went so far as to recommend that succinylcholine should only be used in situations demanding urgent intubation and that concerns of anaphylaxis associated with rocuronium should be kept in mind with each planned use.

Why do muscle relaxants cause anaphylaxis? All of these agents contain at least one substituted ammonium group, and this group is believed to be the source of cross-sensitivity that can occur following exposure to a variety of personal care products, such as shampoo, toothpaste, detergent, and even some over-the-counter medications. For instance, pholcodine an over-the-counter antitussive agent available in Europe has also been implicated in cross-sensitivity reactions. After Norway removed pholcodine from the market in 2008, they've observed a significantly lower incidence of muscle relaxant induced anaphylaxis (1, 2).

Is there a role for sugammadex in rocuronium-induced anaphylaxis? If we think back to Joan in the case study, you'll recall that she received sugammadex. This choice was informed by a 2012 case report that described a successful resuscitation of rocuronium-induced anaphylaxis that included sugammadex. The clinicians involved in that case advanced the view that the encapsulation of rocuronium by sugammadex may have selectively eliminated the antigenic properties of rocuronium (1). It must be cautioned that this approach, though described in the literature, is controversial at this time. Whether this treatment gains traction in the future remains to be seen.

## The "Test Dose"

When a patient's alleged allergy is under question, some anesthesia providers opt to challenge the patient with a "test-dose" under the belief that this practice will, at worst, provoke a minimal and easily remedied physiologic response. The other side of the aisle argues that the physiologic response to an antigen is dose-independent, so even a small amount of antigen can produce a life-threatening reaction. In which camp do you belong? Are your beliefs supported by the current state of the science? Let's turn to the allergy and immunology literature to learn more.

Performed under immediate surveillance, the drug provocation test (DPT) is used to detect a patient's response to a potential allergen. The DPT might use the drug in question, a structurally similar drug, or even an alternative compound with known diagnostic value. The very idea of the DPT is controversial, and in many instances, the test procedures are not validated (1). Additionally, false-positive results are not uncommon, and they tend to overestimate the true scope of the problem.

While skin testing is the gold-standard, DPT may involve a variety of administration routes including oral, topical, conjunctival, and parenteral (IV, IM, SC). The period of time one waits to observe allergic phenomena is dependent on numerous variables including characteristics of the drug, the nature of the reaction, patient-related factors such as co-administered medications. It's common to begin with an extremely low dose (a dose far lower than what is commonly utilized "test-dose" given in the operating room) and carefully increasing it and stopping as soon as the first objective signs occur. One must also appreciate that a true DPT may require hours, days, or even weeks depending on the drug in question (2).

What does this mean for anesthesia providers? Simply stated, it is near impossible to properly conduct DPT in the operating room, because administering a small dose that's followed by the full, therapeutic dose shortly thereafter is not equivalent to a properly executed DPT. Instead, the patient is best served by consultation with an allergist. When confronted with the decision to administer a "test-dose" in the operating room, the most prudent approach is to select a preservative-free

formulation of an alternative agent that does not exhibit cross-sensitivity to the drug in question.

## Cephalosporin In the PCN Allergic Patient

A patient says she may have experienced a reaction to penicillin as a child. The surgeon orders cefazolin and suggests you administer a test-dose after anesthetic induction. How do you proceed and why?

Cephalosporins are commonly indicated as first-line prophylaxis against surgical site infection. A commonly perpetuated myth suggests that the rate of cross-reactivity between penicillin and cephalosporins is as high as 10%. Today, we recognize that the true incidence is < 1% (1). The risks associated with cross-sensitivity must be carefully balanced against the risks of selecting a second-line agent as well as the implications of antibiotic resistance.

Why is there cross-sensitivity between PCN and cephalosporins? Both classes share a beta-lactam ring in their chemical structures. While this ring was previously implicated as the origin of cross-sensitivity, we've come to understand that the R1 side chain that extends from the ring is the most likely culprit. Therefore, we can reduce the incidence of cross-sensitivity reactions by selecting a cephalosporin whose R1 side chain is structurally dissimilar to penicillin.

What should you do if a patient reports an allergy to PCN? If the patient reports a history of rash or other signs of intolerance (such as nausea and vomiting), then it is reasonable to administer cefazolin or a 3rd or 4th generation cephalosporin, as these agents have structurally dissimilar side chains from penicillin (2). If the patient reports a history of an IgE mediated event (as evidenced by urticaria, bronchospasm, or anaphylaxis) or exfoliative dermatitis (such as Stevens-Johnson syndrome), a conservative approach suggests that the patient should receive a non-beta-lactam antibiotic such as vancomycin or clindamycin.

In any case, some clinicians administer the preoperative antibiotic prior to anesthetic induction. The benefit is that the awake patient can report symptoms of hypersensitivity and the ability to examine the patient is not encumbered by the surgical drapes. One must be careful, however, as the time between antibiotic administration and surgical incision may exceed the time requirements mandated by the SCIP protocol. In this instance, a patient would require a second dose of the antibiotic, possibly introducing additional risks.

## Key Points

Muscle relaxants, latex, and antibiotics are the commonest causes of anaphylaxis in the operating room, although there is a wide variety of triggers to which the patient is exposed perioperatively.

It can be difficult to detect many of the clinical signs of anaphylaxis under anesthesia, and those that present are commonly attributed to other causes.

The magnitude of an anaphylactic reaction is dose-independent. Therefore, even a sub-therapeutic dose of antigen can give rise to a life-threatening reaction. Consider this, a woman with a milk allergy suffered fatal anaphylaxis following inhalation exposure to milk protein after entering a milk storage room in a barn!

The cornerstones of anaphylaxis treatment include stopping antigen exposure, airway management with 100% oxygen, epinephrine, and aggressive fluid resuscitation.

There continues to be controversy about whether to administer a cephalosporin to a patient with a history of penicillin allergy. Unless a patient experienced an IgE reaction to PCN, it is reasonable to administer cephazolin or a 3rd or 4th generation agent.

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