

Anaphylactic Reaction With Avitene: A Pediatric Case Report

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Anaphylaxis is an unanticipated severe allergic reaction that can occur during a surgical procedure. A patient is exposed to myriad foreign substances during surgery, such as anesthetic drugs, blood products, and surgical materials, including a commonly used hemostatic agent called Avitene Microfibrillar Collagen Hemostat. Anaphylaxis is the most severe immune-mediated reaction, and it generally occurs on reexposure to a specific antigen.

This case report details a case of an acute anaphylactic reaction in a 10-year-old boy presumed to be

from Avitene used during a routine ear, nose, and throat surgery. There will be a discussion of the mechanism and management of anaphylaxis as well as a brief overview of hemostasis and hemostatic agents. Education of anesthesia providers and the surgical team may enable early detection and management of anaphylactic reactions that may improve patient outcomes and save lives.

Keywords: Anaphylaxis, Avitene, hemostasis, hemostatic agent.

Anaphylaxis is an unanticipated severe allergic reaction that can occur during a surgical procedure. A patient is exposed to myriad foreign substances during surgery, such as anesthetic drugs, blood products, and surgical materials.

This case report details a case of an acute anaphylactic reaction in a 10-year-old boy presumed to be from a microfibrillar collagen hemostat (Avitene) used during a routine ear, nose, and throat (ENT) surgery.

Case Summary

A 10-year-old boy, measuring 44.5 kg in weight and 146 cm in height, presented for a repair of an alveolar cleft with bone graft from an iliac crest repair of an oral nasal fistula. The medical history had normal findings. The surgical history included several procedures for cleft lip and palate repair and an odontectomy. No anesthesia or surgical complications had been noted. The boy was not receiving any medications. Results of a preoperative assessment revealed an ASA physical status 1.

On arrival at the operating room, standard monitors were applied, and a mask induction was initiated with a blend of 4 L of oxygen, 6 L of nitrous oxide, and 6.0% of sevoflurane. A 20-gauge peripheral intravenous (IV) catheter was inserted in the left hand, and 50 µg of fentanyl, 50 mg of propofol, 25 mg of rocuronium, and 8 mg of dexamethasone (Decadron) were given IV through an infusion of lactated Ringer's solution. Under direct laryngoscopy with a MacIntosh size 2 blade, a 6.0-mm cuffed oral endotracheal (ET) tube was placed. Placement of the ET tube was confirmed by bilateral breath sounds

and positive end-tidal carbon dioxide (ETCO₂). An esophageal temperature probe was inserted, and general anesthesia was maintained with 6% to 8% end-tidal desflurane and 2 L of oxygen.

The supine position was used for surgery, and a lower body warming device was applied. Once positioning was accomplished, 100 µg of fentanyl and 1 g of cefazolin were administered IV. The first part of the surgery was uneventful. The surgeon inserted a throat pack and initially focused attention on the exposure of the alveolar cleft and repair of the fistula. The second part of the surgery involved harvesting the right anterior iliac crest bone graft. Cancellus bone (6 mL) was harvested, with no evidence of any substantial bleeding. The defect in the iliac crest was then filled with Avitene.

Several minutes after the surgeon inserted the Avitene, the peak airway pressures increased from 18 to 45 mm Hg. The ETCO₂ decreased from 30 mm Hg to 20 mm Hg, the heart rate increased from 72/min to 108/min, and the blood pressure decreased from 108/40 mm Hg to 60/20 mm Hg. The Certified Registered Nurse Anesthetist (CRNA) asked the surgeon to remove the Avitene from the iliac crest. Then the wound was irrigated with normal saline. The desflurane administration was turned off, and 3 boluses of 30 µg of epinephrine were administered IV. The IV fluids were opened, and an albuterol inhaler was aerosolized via the ET tube. An epinephrine infusion was initiated at a rate of 4 µg/min, then quickly increased to 8 µg/min.

Within 30 minutes, the heart rate, blood pressure, and peak pressures returned to baseline, and general anesthesia was maintained with desflurane. The epinephrine infusion rate was decreased to 2 µg/min for maintenance.

Results of an arterial blood gas analysis were obtained and revealed the following values: pH, 7.21; PaCO₂, 53 mm Hg; PaO₂, 412 mm Hg; HCO₃⁻, 21.3 mEq/L; BE, -7 mmol/L, and SaO₂, 100%. There was discussion with the surgeon about stopping the surgery. A decision was made to continue, after the patient stabilized to close the iliac crest.

Attention was then turned to the oral defect. The harvested bone was placed in the alveolar process. The throat pack was removed, and the incision was closed. An additional 4 mg of dexamethasone and 25 mg of diphenhydramine (Benadryl) was administered IV. A total of 1,500 mL of crystalloid was administered throughout the case. Total surgical time was 4 hours and 16 minutes.

Because of diffuse facial and tongue swelling, and an inability to wean the patient off a regimen of vasopressors, it was determined that it was most appropriate for this patient to be transferred to a hospital with a level I pediatric intensive care unit (PICU). A decision was made by the anesthesia team to have the intubated patient admitted to the nearer postanesthesia care unit (PACU) rather than transferred to the remote adult 24-bed surgical intensive care unit. A propofol infusion was initiated at 75 µg/kg/min for sedation, and an epinephrine infusion at 2 µg/min was continued for maintenance. In the PACU, the patient was placed on synchronized intermittent mandatory ventilation therapy with a tidal volume of 300 mL, rate of 6/min, positive end-expiratory pressure (PEEP) of 5 cm H₂O, and pressure support of 8 cm H₂O. The anesthesia team involved in the care of the patient initially stayed with the patient. Eighty minutes later, the patient was transferred to a level I pediatric trauma center via helicopter.

The patient remained intubated for 24 hours but was extubated the following day (according to the surgeon). No report could be recovered from the receiving PICU or additional hospital stay. He was discharged from the outlying hospital on postoperative day 2. The anesthesiologist called the patient 1 week later. The patient recovered fully without sequelae and thanked the anesthesia team for the care given.

Discussion

This case report describes our experience in caring for a pediatric patient with an acute anaphylactic reaction during surgery. This reaction occurred quickly and without warning. Our anesthesia team was well prepared and recognized the symptoms immediately. The purpose of this case study is to review the mechanism of anaphylaxis and most importantly, how to manage it. In addition, there will be a review of the offending hemostatic agent and a brief synopsis of hemostasis in the hope of preparing other anesthesia teams for this potential complication.

• **Mechanism of Anaphylaxis.** A patient is exposed to myriad foreign substances during surgery, such as

anesthetic drugs, blood products, and surgical materials, including a commonly used hemostatic agent called Avitene. All can have the potential to trigger anaphylaxis, a life-threatening allergic reaction. Anaphylaxis is the most severe immune-mediated reaction, which generally occurs on reexposure to a specific antigen. Although antibiotics, muscles relaxants, and latex account for most cases of anaphylaxis during the perioperative period, there can be adverse effects from collagen-based agents as well.¹ Most are infrequent, but serious adverse events are often reported with Avitene.²

Anaphylactic reactions are due to the acute and massive release of cardiac mediators from the mast cells and basophils.³ Activation of mast cells and basophils are mediated by the interaction of an allergen with immunoglobulin E (IgE). The first time an individual is exposed to an antigen, specific IgE antibodies are formed in response to the foreign antigen. These antibodies bind to mast cells and basophils. With each exposure to the antigen, epithelial or endothelial barriers are invaded, allowing the antigen access to the IgE antibodies on the presensitized mast cells or basophils. A rapid release of potent chemical mediators occurs. Cardiac mast cells release renin that activates the renin angiotensin system, which increases arterial vasoconstriction.⁴ Angiotensin I is converted to angiotensin II by angiotensin converting enzyme. This is the primary mechanism that ultimately is responsible for cardiac arrhythmias, myocardial infarction, and sudden death associated with anaphylaxis.⁴

After activating the mast cells or basophils, histamine is predominately released along with other mediators, such as prostaglandin D₂, leukotrienes, platelet-activating factor, tryptase, and eosinophils.³ These mediators are responsible for the signs and symptoms that are presented in an acute anaphylactic reaction. Histamine stimulates vasodilation, heart rate, cardiac contraction, and glandular secretion. Prostaglandin D₂ acts as a bronchoconstrictor, pulmonary and vascular constrictor, and peripheral vasodilator. Leukotrienes and platelet-activating factor increase bronchoconstriction and vascular permeability.³

Symptoms progress rapidly and can affect most organ systems (Table 1). Cutaneous signs include pruritus and flushing. It also affects the upper and lower airway with angioedema, rhinitis, and bronchoconstriction with wheezing and cyanosis. It involves the intestinal tract with abdominal pain, nausea, vomiting, and diarrhea. Cardiovascular manifestations include hypotension, shock, cardiac arrhythmias, ventricular dysfunction, and cardiac arrest.⁵ Because patients are under surgical drapes and are under general anesthesia or are sedated, the early signs of anaphylaxis often go unrecognized, leaving bronchospasm and cardiovascular collapse as the first recognized signs of anaphylaxis.¹

• **Management of Anaphylaxis.** The management of anaphylaxis consists of the immediate discontinuation

Skin, subcutaneous tissue, and mucosa^{a,b,c}

Flushing, itching, urticaria (hives), angioedema, morbilliform rash, pilor erection
Periorbital itching, erythema and edema, conjunctival erythema, tearing
Itching of lips, tongue, palate, and external auditory canals; and swelling of lips, tongue, and uvula
Itching of genitalia, palms, and soles

Respiratory^a

Nasal itching, congestion, rhinorrhea, sneezing
Throat itching and tightness, dysphonia, hoarseness, stridor, dry staccato cough
Lower airways: increased respiratory rate, shortness of breath, chest tightness, deep cough, wheezing/bronchospasm, decreased peak expiratory flow
Cyanosis
Respiratory arrest

Gastrointestinal^a

Abdominal pain, nausea, vomiting (stringy mucus), diarrhea, dysphagia

Cardiovascular system^a

Chest pain
Tachycardia, bradycardia (less common), other arrhythmias, palpitations
Hypotension, feeling faint, urinary or fecal incontinence, shock
Cardiac arrest

Central nervous system^a

Aura of impending doom, uneasiness (in infants and children, sudden behavioral change, eg, irritability, cessation of play, clinging to parent); throbbing headache (pre-epinephrine), altered mental status, dizziness, confusion, tunnel vision

Other^a

Metallic taste in the mouth
Cramps and bleeding due to uterine contractions in females

Table 1. Symptoms and Signs of Anaphylaxis

(Permission to reprint from *World Allergy Organization Journal*.⁶)

^aSudden onset of symptoms and signs is characteristic of anaphylaxis.

^bThe purpose of listing signs and symptoms in this Table is to aid in prompt recognition of the onset of anaphylaxis and to indicate the possibility of rapid progression to multi-organ system involvement, not to grade severity.

^cSkin and mucosal symptoms are reported to occur in 80% to 90% of patients with anaphylaxis, respiratory tract involvement in up to 70%, gastrointestinal tract involvement in up to 45%, cardiovascular system involvement in up to 45%, and central nervous system involvement in up to 15%.

Note: Symptom patterns vary from one patient to another, and even in the same patient, from one anaphylactic episode to another. Only a few symptoms might be present.

Medications

First line (priority) medication

Epinephrine (adrenaline) 1:1,000 (1 mg/mL) for intramuscular injection 0.01 mg/kg, to a maximum of 0.5 mg (adult), 0.3 mg (child)

Second line medications

H₁-antihistamine for intravenous infusion eg, chlorpheniramine 10 mg (adult), 2.5-5 mg (child) or diphenhydramine 25-50 mg (adult) (1 mg/kg, maximum 50 mg [child])

β₂-adrenergic agonist, eg, salbutamol (albuterol) solution, 2.5 mg/3 mL or 5 mg/3 mL (adult), (2.5 mg/3 mL [child]) given by nebulizer and face mask glucocorticoid for intravenous infusion, eg, hydrocortisone 200 mg (adult), maximum 100 mg (child); or methylprednisolone 50-100 mg (adult); 1 mg/kg, maximum 50 mg (child)

H₂-antihistamine for intravenous infusion, for example, ranitidine 50 mg (adult) or 1 mg/kg, maximum 50 mg (child)

Table 2. Medications, Supplies, and Equipment for Anaphylaxis Treatment

(Permission to reprint from *World Allergy Organization Journal*.⁶)

of the allergen, interrupting the effects of the released mediators and preventing more mediator release.¹ The anesthesia provider must react immediately because an anaphylactic reaction can be life-threatening if undetected. The gold standard of treatment after removal of the antigen is epinephrine. According to the World Health Organization, epinephrine is classified as an es-

sential medication for treatment of anaphylaxis (Table 2).⁶ Epinephrine is the drug of choice in the treatment of anaphylaxis because its α₁-adrenergic effects help to support the blood pressure by increasing peripheral vascular resistance. The β₁-adrenergic effects increase heart rate and contraction, thus increasing cardiac output. The β₂-adrenergic effects bronchodilate and inhibit the

release of inflammatory mediators.⁷ Epinephrine can be used as a bolus at a dose of 0.01 mg/kg or an infusion at 0.01 to 0.05 mg/kg/min.¹ In this case study, after the initial epinephrine boluses were given in the operating room (OR), an epinephrine infusion was necessary to maintain the patient's blood pressure.

Severe episodes of anaphylaxis often involve the cardiovascular system and result in tachycardia and decreased arterial blood pressure. Treatment should include not only epinephrine but also volume support and adjuvant medications. Replacement fluids of 20 mL/kg of IV crystalloid must be given to compensate for the peripheral vasodilation.⁸ An inhaled β_2 -agonist such as albuterol and ipratropium bromide nebulizers are very useful in treating bronchospasm associated with anaphylaxis. It is possible that the delivery of the nebulizers may be impaired because of the bronchospasms, and systemic epinephrine must still be considered the first drug of choice.⁸ Also, airway support with 100% oxygen will increase oxygen delivery and compensate for the increased oxygen consumption resulting from the shock.¹

Histamine-1 antagonists should be given promptly in the early phases of an allergic reaction, but there is no evidence of their usefulness in acute anaphylaxis.⁹ According to a Cochrane systematic review, no high-quality evidence from randomized controlled trials was found to support the use of H_1 -antihistamines in treatment of anaphylaxis.⁹ Histamine-1 blockers (diphenhydramine) and H_2 -blockers (ranitidine or cimetidine) can be used but should never delay the administration of epinephrine. It is important to note that antihistamines have a slow onset of action and cannot block events that occur subsequent to histamine receptor binding.³

A Cochrane systematic review also failed to identify any evidence from randomized controlled trials to confirm the effectiveness of corticosteroids in the treatment of anaphylaxis.⁹ Corticosteroids (hydrocortisone) should not be considered as a first line of treatment but can be given in the later phases to reduce airway swelling.⁸ Extubation should be delayed because airway swelling and inflammation may continue for 24 hours.¹⁰

An observation period is indicated for all patients experiencing an anaphylactic reaction. Latent reactions as long as 72 hours can occur in up to 20% of the patients. It is suggested that patients should be observed anywhere from 6 to 24 hours depending on the severity of the reaction.³

• **Hemostatic Agents.** It is presumed that the anaphylactic reaction was caused after Avitene was inserted in the iliac crest to aid in hemostasis. The reaction occurred immediately. We present a review of why hemostatic agents are used in the OR and their mechanisms of action.

Surgical bleeding adds a number of complications, such as poor surgical vision in the field, unstable hemodynamics, increased need for blood transfusions, increased operative time, and increased overall mortality.

Factors to consider when selecting a topical hemostat include the type of surgery, the size of the wound, and accessibility of the site. In addition, other factors may include the severity of the bleeding and the coagulation status of the patient.

Hemostasis can be achieved in other ways if the body cannot do it naturally. Although natural hemostasis is most desired, having other means of achieving hemostasis is vital for survival. Hemostasis is of critical importance during all surgical procedures. Hemostasis can be achieved chemically with epinephrine. Epinephrine (1:50,000 or 1:100,000) can be added to the local anesthetic to prolong the effects of the local anesthetic and to reduce bleeding in the operative field.¹¹ It can also be controlled mechanically, which includes manual pressure, ligature, and the application of a tourniquet. Intraoperative interventions also include sutures and heat-generating cautery devices such as electrocauterization or laser cauterization. Unfortunately, these may create areas of necrotic tissue, which may lead to impaired healing.¹² Heat-generating methods are sometimes insufficient or inappropriate for a specific procedure or anatomic location, leading to the development of other adjunctive therapies, including topical hemostats.

The ideal topical hemostat would provide prompt control of bleeding, can be stored at room temperature, be preparation free, and can be used in a variety number of cases. A number of different agents have been developed to aid surgical hemostasis. Topical hemostats are classified into 4 categories: mechanical hemostats, active hemostats, flowable hemostats, and fibrin sealants,¹³ which are summarized in Table 3.¹⁴ For the sake of this article, we will discuss mechanical hemostats only.

Mechanical topical hemostat products are gelatin, collagen, cellulose, and polysaccharide based. Mechanical hemostats are applied as sponges or as a powder. They produce swelling and cause a mechanical barrier to bleeding and oozing. They can be used with saline or thrombin and can be stored at room temperature. Mechanical products are generally used as first-line agents because they are the least expensive topical hemostat and are widely available.¹³

Bovine collagen products include Avitene and Ultrafoam. Avitene and Ultrafoam are the only collagen hemostats indicated for all surgical procedures.¹⁵ In addition to mechanical cessation of bleeding, collagen affects the coagulation process. It is known to cause aggregation of platelets, degranulation, and the release of coagulation factors, which enables the formation of fibrin. Bovine collagen products are commonly combined with procoagulant substance, often thrombin.¹⁶ Avitene is effective in controlling arterial bleeding in patients, with platelet counts as low as $20,000 \times 10^3/\mu\text{L}$. It comes in the form of flour in a syringe or in a woven sheet. It is designed to control bleeding in open surgeries and to access deep

Class	Product	Manufacturer
MECHANICAL		
Porcine	Gelfoam (absorbable gelatin powder)	Pfizer Injectables (Pharmacia & Upjohn)
Porcine	Surgifoam (absorbable gelatin sponge, USP)	Johnson & Johnson (Ethicon)
Bovine	Avitene (collagen sponge)	Davol
Bovine	Ultrafoam (collagen sponge)	Davol
Cellulose	Surgicel (absorbable hemostat)	Johnson & Johnson (Ethicon)
Cellulose	Surgicel Fibrillar (absorbable hemostat)	Johnson & Johnson (Ethicon)
Cellulose	Surgicel Nu-Knit (absorbable hemostat)	Johnson & Johnson (Ethicon)
Polysaccharide sphere	Arista (absorbable hemostatic particles)	Medafor
ACTIVE		
Thrombin	Thrombin-JMI (thrombin, topical [bovine], USP)	King Pharmaceuticals Inc.
Thrombin	Evithrom (thrombin topical [human])	Johnson & Johnson (Ethicon)
Thrombin	Recothrom (thrombin, topical [recombinant])	ZymoGenetics
FLOWABLES		
Bovine gelatin + HPP thrombin	FloSeal (hemostatic matrix)	Baxter Healthcare Corporation
Porcine gelatin + thrombin	Surgiflo (hemostatic matrix)	Johnson & Johnson (Ethicon)
FIBRIN SEALANTS		
PH thrombin, PH fibrinogen, syn aprotinin, plasminogen	Tisseel (fibrin sealant)	Baxter Healthcare Corporation
PH thrombin, HFC, albumin	Evicel (fibrin sealant [human])	Johnson & Johnson (Ethicon/Omrix)

Table 3. Topical Hemostats^a

(Permission to reprint from the *US Pharmacist*.¹⁴)

Abbreviations: HFC, human fibrinogen concentrate; HPP, human pooled plasma; PH, pooled human; syn, synthetic.

^aRefer to manufacturer's package insert for each product.

penetrating wounds, particularly in neurosurgery and ENT procedures.¹⁷

In addition to Avitene, the patient was exposed to another collagen-based agent called CollaPlug during one of the previous oral surgeries. CollaPlug is used in many dental procedures such as exodontia, tissue biopsies, endosseous implants, and periodontal surgery.¹⁶ It is a hemostatic agent used to decrease the amount of bleeding in dental surgeries and is valuable for certain patient groups with coagulation defects.¹⁶ It is also made from bovine collagen and is a highly porous sponge that absorbs blood and wound exudate. CollaPlug is indicated for wound protection and to control oozing or bleeding from clean oral wounds.¹⁷ Products should be held in place for approximately 2 to 5 minutes to achieve hemostasis and then may be removed, replaced, or left in situ. It is completely reabsorbed within 14 to 56 days.¹⁸ It is presumed that because of this patient's previous exposure to CollaPlug, the patient had formed IgE antibodies to collagen and, therefore, the patient had a severe anaphylactic reaction to Avitene.

Adverse effects of collagen-based agents are rare but may occur. Serious adverse reactions to these agents are reported most often with Avitene.¹⁹ Other adverse events associated with unspecified collagen agents include ad-

hesion formation, allergic reactions, and, more severely, unexplained cases of brain injury.²⁰ Extensive in vitro and in vivo investigations were performed in these collagen products. It was concluded that collagen-containing blood, if returned to the circulation by either pump suction or cell-salvage devices, may pass 40- μ m pore size filters and lodge in vital organs such as the brain.²¹ Therefore, it is recommended that the collagen-containing blood that is intended to be collected and returned to the patient circulation should not be used.

• **Review of Hemostasis.** Maintaining hemostasis during any surgical procedure is vitally important. Hemostasis occurs when blood is present outside the blood vessels because of injury or surgery. This is a complex process requiring coordinated activation of platelets and plasma clotting factors to form a platelet-fibrin clot. During hemostasis, 3 steps occur in rapid sequence. Vascular spasm is the first response as the blood vessels constrict to allow less blood to be lost. The second step involves the platelet response, in which the platelets stick together to form a temporary seal. The third and last step is coagulation. Coagulation reinforces the platelet plug with fibrin threads that act as glue.²²

Vascular spasm is triggered by chemicals released by endothelial cells and platelets, and initiated by local pain

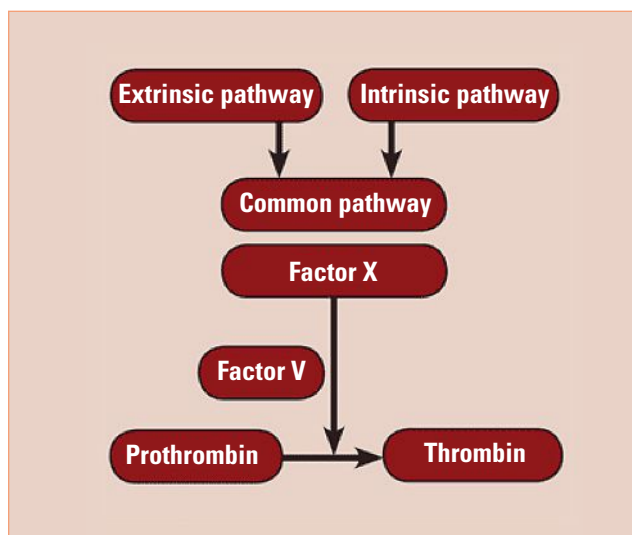


Figure. Coagulation Cascade

(Permission to reprint from *US Pharmacist*.¹⁴)

Note: Thrombin-containing hemostats stimulate activity in the coagulation cascade and promote the conversion of fibrinogen to fibrin.

receptors. In primary hemostasis, within seconds of a blood vessel's epithelial wall being disrupted, platelets begin to aggregate to the subendothelial surface. As platelets adhere to the collagen fibers, they release adenosine diphosphate (ADP), serotonin, and thromboxane A₂. These chemicals are released to cause more platelets to stick to the area and release more chemicals creating a plug.²² In secondary hemostasis, clots form upon the conversion of fibrinogen to fibrin in addition to the platelet plug. The platelet plug formation is activated by a protein called von Willebrand factor. The last step is the coagulation cascade (Figure). Coagulation reinforces the platelet plug with fibrin threads. When this occurs the clotting factors begin to form fibrin. Coagulation uses fibrin threads to act as glue for the sticky platelets. The release of prothrombin also plays an essential part in the coagulation process because it allows for the formation of a thrombus, or clot. This final step forces blood cells and platelets to stay trapped in the wounded areas, which ultimately decreases bleeding.²²

Conclusion

There are no accurate data regarding pediatric anaphylaxis in the United States because of many insufficient studies and failure to report serious and fatal events.²³ A report from 2001 estimated that anaphylaxis might affect 1.2% to 16.8% of the total US population and that 0.02% of the population may die of anaphylaxis.²⁴ Children who have a history of asthma and allergies are at much higher risk of anaphylaxis, as are individuals with a previous anaphylactic reaction.²³

Anaphylaxis is a continuing problem for anesthesia

providers, and its effects can be devastating. Education regarding prevention, evaluation, early recognition, and treatment is important. Anaphylactic reactions are a continuing challenge, but rapid diagnosis and treatment are important in preventing adverse clinical outcomes. Documentation of anaphylaxis during anesthesia, referral to an allergist for identification of the allergen, and appropriate labeling in the patient's medical record and on an identification bracelet are essential to prevent future episodes of anaphylaxis.

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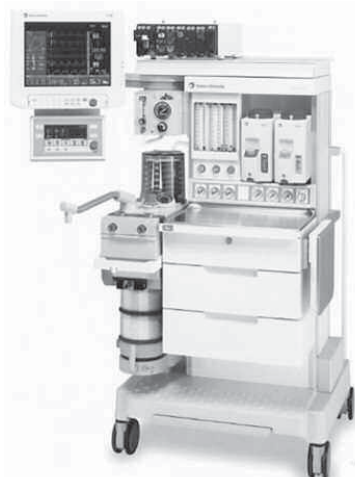
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