Vaccine Induced Anaphylaxis

Tim Hackett, DVM, MS
Diplomate ACVECC
Assistant Professor of Emergency and Critical Care Medicine
Colorado State University
Fort Collins, Colorado

Veterinary vaccines have had profound beneficial effects in animal health. However, with manipulation of the immune system, systemic reactions can result. Immunologic reactions do occur and are related to either hypersensitivity or autoimmunity. Immunologic reactions are classified as types I, II, III, or IV and all types can occur as the result of vaccination.

Type I reactions are the acute hypersensitivity reactions. The most life threatening of these events, anaphylaxis, must be recognized quickly and treated properly to prevent systemic complications and death. Although called immediate hypersensitivity, these reactions can be delayed several hours.

Anaphylaxis reactions result from an IgE response to an antigen. The IgE binds to the surface of mast cells and basophil cells. Upon subsequent exposure to the same antigen (as in a booster vaccination), mast cell degranulation results in the release of inflammatory mediators causing severe hypotension with multiorgan complications. Anaphylaxis results in cardiovascular collapse with serious consequences in the gastrointestinal tract and lungs of small animals. The actual incidence of anaphylaxis following immunization in small animals is unknown. With the use of adjuvanted and multivalent vaccines, practitioners need to recognize the signs of anaphylaxis in order for treatment to be effective. In addition to quick treatment, clinicians need to report any adverse reactions (see On the News Front).

Articles with this symbol provide standards for canine patients.
Articles with this symbol provide standards for feline patients.
Articles with both symbols cover canine and feline topics.

DIAGNOSTIC CRITERIA

Historical Information

- Recent vaccination. Type I hypersensitivity reactions can occur within minutes to several hours after vaccination. Although any vaccine can induce anaphylaxis, it is most often associated with Leptospira bacterin, inactivated adjuvanted rabies, FeLV, or respiratory vaccines. These vaccines are adjuvanted or multivalent and contain large amounts of foreign protein.

- Age/gender predisposition. Anaphylactic reactions can occur in puppies and kittens after their second or third vaccination. Not limited to young animals, these reactions can occur in any age on subsequent exposure to a vaccine antigen. No gender predisposition known.

- Breed/species predisposition. At least one author has reported an increasing frequency in type I hypersensitivity reactions in cats. This fact may be due to the increasing use of inactivated adjuvanted vaccines for rabies, feline respiratory diseases, FPV and FeLV. In dogs, the miniature Dachshund is over-represented in cases of immunologic vaccine
reactions. At least one author (Greene, 1998) recommends avoiding inactivated, highly adjuvanted vaccines and intramuscular injection in favor of modified live vaccines and reducing the number of antigens given simultaneously in this breed.

**Physical Examination Findings**

**Systemic anaphylaxis.** Anaphylaxis resulting from generalized release of mast cell mediators is the most severe hypersensitivity reaction. Clinical presentation will vary with species as different shock organ systems are affected. Most will show signs of cardiovascular collapse as mast cell degranulation and the release of inflammatory mediators result in severe hypotension and shock.

**Feline anaphylaxis.** Cats with vaccine induced anaphylaxis frequently present with the following signs:
- Facial pruritus.
- Ptyalism.
- Tachypnea (>30 breaths/minute), open mouth breathing, and cyanosis are frequently reported in the most severely affected cats. The lungs are the primary shock organ of cats and the release of inflammatory mediators causes laryngeal edema, severe bronchoconstriction, and pulmonary edema.
- Collapse.
- Vomiting and bloody diarrhea can also be seen in cats presented for vaccine associated anaphylaxis.

**Canine anaphylaxis.** Clinical problems in dogs presented for acute hypersensitivity reactions include:
- Vomiting/diarrhea.
- Hypotension (Systolic blood pressure < 90 mmHg).
- Tachycardia (>120 beats per minute).
- Weakness.
- Facial edema.
- Pruritus.

**Laboratory Findings**

Laboratory testing is of limited value for acute hypersensitivity reactions. Quick recognition of signs and immediate treatment is required to prevent organ failure and death associated with systemic anaphylaxis. Abnormal findings reflect affected organ systems. After emergency treatment for anaphylaxis, patients should be monitored closely for signs of organ failure. Blood gas parameters will be useful to evaluate respiratory function while complete blood counts and serum biochemical profiles will identify potential organ dysfunction.

**Other Diagnostic Findings**

**Blood pressure.** Indirect blood pressure measurement will give the clinician useful information in treating anaphylaxis. Hypotension (systolic blood pressure <90
mmHg) is a relatively specific sign of anaphylaxis. Reliable blood pressure monitoring will help guide therapy.

- **Radiography.** Animals showing signs of anaphylactic shock should not be stressed with radiographs. However, dogs and especially cats can develop pulmonary complications associated with vaccine induced anaphylaxis. Thoracic radiographs may reveal interstitial and alveolar patterns consistent with pulmonary edema and pulmonary hemorrhage.

**Summary of Diagnostic Criteria**

Any abnormal behavior in the minutes to hours following vaccination should be investigated and the animal closely monitored for signs of facial edema and cardiopulmonary dysfunction. The following findings are consistent with anaphylaxis and warrant immediate treatment:

- Dyspnea.
- Hypotension.
- Vomiting.
- Weakness.
- Facial swelling.
- Facial pruritus.

**Differential Diagnoses**

Travel to and from the veterinarian can be stressful. Animals with underlying cardiopulmonary disease or conditions such as hypoadrenocorticism may suffer acute exacerbation of quiescent problems. Depending on the organ system affected, some of the following differential diagnoses should be considered:

- Dilative cardiomyopathy.
- Hypertrophic cardiomyopathy.

**TREATMENT RECOMMENDATIONS**

**Initial Treatment**

Generalized anaphylaxis is a medical emergency. Treatment must be directed at improving oxygen delivery by reversing circulatory collapse and the pulmonary effects of systemic mast cell degranulation.

**Oxygen supplementation.**

In a patient with severe hypoxia, pulmonary edema, or hypoventilation (PCO₂ > 50 mmHg), a ventilator with positive pressure ventilation may be necessary. In less severely affected, shocky patients, supplemental oxygen will improve tissue oxygen delivery. An oxygen cage can increase the partial pressure of oxygen in inspired air. This can also be accomplished at reduced cost by face mask or nasal insufflation.

**Intravenous access.** Hypotension due to vasodilation and increased vascular permeability requires IV fluids and drugs. IV catheterization preferably with a central catheter is vital and should be considered a priority in management.

**Epinephrine.** Epinephrine improves blood pressure and cardiac output through α–adrenergic increases in systemic vascular resistance. The β–adrenergic effects of epinephrine include bronchodilation, improved heart rate, and contractility. Epinephrine also antagonizes mast cell degranulation by increasing intracellular cyclic adenosine monophosphate. The dose of epinephrine for anaphylaxis is 0.01 to 0.02 mg/kg IV in severe cases, IM or SQ in less severe cases. The dose of epinephrine can be repeated in 15–20 minutes if necessary.

**Crystalloid fluid therapy.** IV fluid therapy should be instituted immediately with lactated Ringers solution or 0.9% NaCl at a shock rate (1 blood volume of crystalloid fluids in one hour). Dogs can receive as much as 90 ml/kg in one hour. Cats, with smaller relative blood volumes than dogs, should receive 45 ml/kg of crystalloid fluids in the first hour. To avoid overhydration, central venous pressure and thoracic auscultation should be repeated. During an IV fluid challenge, the central venous pressure should be 3–5 cm H₂O. The dose of crystalloid fluids can be titrated by monitoring blood pressure and heart rate. The first ¼ of the calculated shock dose should be given rapidly (over 10 minutes). After receiving this titrated dose, response is evaluated (heart rate, blood pressure, mentation). If the patient is still shocky, another ¼ of the total shock fluids is given over 20 minutes. After the second ¼ dose, in addition to rechecking subjective signs of shock, the packed cell volume and serum total solids should be re-evaluated. If the total solids have dropped to less than 4 gm/dl, a colloid may be necessary. If the packed cell volume drops acutely and the patient would benefit from added hemoglobin, whole blood, packed red blood cells, or cell free hemoglobin (Oxyglobin®, Biopure) may be necessary.

**Synthetic colloids.** Hetastarch (Hespan®, Dupont Critical Care) or Dextran (6% Gentran 70®, Baxter Healthcare) may prolong the hemodynamic response seen with crystalloid fluids. These
products are administered as a 5 ml/kg bolus with a daily dose of 20 ml/kg.

- **Corticosteroids.** Fast acting corticosteroids such as prednisone sodium succinate (Solu-Delta-Cortef®, Upjohn) 10-25 mg/kg IV, or Dexamethasone sodium phosphate @ 2.2 mg/kg IV further inhibit histamine synthesis and phospholipase A₂ activity.®

- **Antihistamines.** Diphenhydramine hydrochloride @ 1 mg/kg IV binds histamine receptors further blocking the effects of mast cell degranulation.®

- **For generalized anaphylaxis,** treatment is started with epinephrine and oxygen supplementation. Epinephrine is repeated as necessary every 15-20 minutes. Hypotension is managed first with IV fluids, followed by corticosteroids and, if necessary, catecholamines. Treatment typically takes less than an hour although monitoring for at least 24 hours is recommended. Heart rate, blood pressure, central venous pressure and urine output should be closely monitored in these patients following resolution of signs. Refractory bradycardia and hypotension may require aggressive treatment with fluids, colloids, catecholamines and atropine.

**Alternative Treatments**

- **Atropine.** Bradycardia or refractory hypotension can be treated with atropine at 0.05 mg/kg IV, IM or SQ, repeated as necessary.

- **Aminophylline.** Administered at 4-8 mg/kg in D5W slowly IV or IM, aminophylline may help relieve bronchoconstriction. Aminophylline should be used cautiously in patients with hypotension. It is reported to be compatible when mixed with dobutamine HCl but is **incompatible** mixed with epinephrine, dobutamine HCl, norepinephrine bitarate, or methylprednisolone sodium succinate. Epinephrine should be administered, if necessary, before aminophylline.

- **Furosemide.** Animals with severe pulmonary edema may benefit from conservative fluid therapy to avoidiatrogenic fluid overload and furosemide at 2.4 mg/kg IV, repeated as necessary. Furosemide is **incompatible** mixed with epinephrine, dobutamine HCl, or antihistamines. Furosemide should be given only after blood pressure has returned to normal.

- **Pressure agents.** After restoration of circulating volume, persistent hypotension can be treated with dopamine (5-20 µg/kg/min IV constant rate infusion), dobutamine (5-20 µg/kg/min), or norepinephrine (2-10 µg/kg/min).

**Supportive Treatment**

- **Oxygen supplementation.** Oxygen is a simple and effective treatment for shock and will enhance oxygen delivery by improving hemoglobin saturation.

- **Cardiac monitoring.** Bradycardia and tachycardia are seen with anaphylactic shock. Epinephrine, dopamine, and aminophylline can cause cardiac arrhythmias and their use warrants close electrocardiographic monitoring.

- **Antibiotics.** Hemorrhagic diarrhea can be seen in dogs and cats following severe hypotensive episodes. Because of the damage to the intestinal mucosa and loss of the normal protective barrier, these animals are at risk of bacterial translocation and sepsis. Broad-spectrum antibiotics are therefore indicated in patients with hemorrhagic diarrhea. Combinations effective against gram-negative enteric pathogens are recommended.

- **Gastrointestinal protectants.** Histamine effects on the GI tract can be reduced with H₂ receptor antagonists like famotidine (Pepcid®, Merck) at 0.5–1.0 mg/kg PO once a day to bid. Other gastrointestinal protectants can be used including sucralfate 0.5–1.0 g PO qid, and Omeprazole (Prilosec®, Astra Merck) at 0.2-0.7 mg/kg PO sid.

- **Antiemetics.** Nausea can contribute to patient discomfort. Metoclopramide given by continuous rate infusion of 1-2 mg/kg/day will reduce central mediated nausea. Chlorpromazine should be avoided due to its potential for α blockade and hypotension. Refractory nausea can be managed with new 5HT3-serotonergic antagonists like ondansetron (Zofran®, Glaxo Wellcome) 0.03 mg/kg SQ or IM qid.

**Localized anaphylaxis**

Mild anaphylaxis is manifested by urticaria, localized angioedema, pruritus, erythema, wheal and flare reactions. Mild GI signs may also be seen. These patients remain alert and normotensive. Treatment for mild anaphylaxis includes diphenhydramine (1-2 mg/kg IV or IM), and dexamethasone sodium phosphate (2.2 mg/kg IV) followed by prednisone (2 mg/kg orally 12-24 hours after initiation to reduce late reactions). Close monitoring is essential, as mild cases can become hypotensive hours later.

**Prevention**

If an animal suffers any hypersensitivity reaction to a vaccination, it is at risk for future reactions and even anaphylaxis if it is
revaccinated and exposed to the offending antigen. To reduce the risk of anaphylaxis the following steps are recommended:

- Use serologic testing to determine the need for further vaccination and reduce or eliminate unnecessary vaccinations.
- For animals with a previous vaccine reaction, antihistamines should be given before subsequent vaccinations.
- Diphenhydramine 1-2 mg/kg IM 15 minutes before vaccination may prevent some effects of mast cell degranulation.
- Animals at higher risk, including miniature Dachshunds and those with previous vaccine reactions, should be observed for several hours, in the veterinarian’s office. Upon returning home they should be kept indoors and observed for 4-6 hours.
- Modify the vaccination schedule to reduce the number of antigens given simultaneously.

- Switch to modified live vaccines and avoid adjuvanted products.
- Use subcutaneous or intranasal formulations instead of intramuscular inoculations.
- Always aspirate the syringe before injecting vaccines to avoid intravascular injection.
- Vaccinate animals early in the visit to allow time to observe any adverse reactions. Animals with no previous vaccine reactions can leave after the physical examination and office call are complete. These owners should be instructed to keep the animals indoors for at least an hour and call should the animal display any unusual behavior.

Patient Monitoring-Home Management

Organ system dysfunction can occur following a severe anaphylactic reaction. Owners should be advised to report any abnormal behavior or symptoms immediately following vaccination. Clients should be instructed to keep their pets indoors and observed for at least 1 hour following vaccination. The following clinical signs warrant an immediate recheck:

- Collapse.
- Dyspnea.
- Vomiting.
- Bloody diarrhea.
- Weakness.
- Anorexia.

The vaccination site should be examined by the owner daily. Any changes, including swelling, redness, or pain should be reported to the veterinarian.

PROGNOSIS

Favorable Criteria

- Facial swelling and pruritus without signs of systemic hypotension.
- Immediate response to therapy (within 30-60 minutes of treatment).

Unfavorable Criteria

- Hypotension.
- Pulmonary edema.
- Hemorrhagic diarrhea.

RECOMMENDED READING


