OVERVIEW
Anaphylactic reactions are among the most acute, life-threatening emergencies we see in practice. Without proper intervention, these patients have high rates of mortality but when treated quickly and appropriately, many if not all may make a full recovery. This presentation will review the pathophysiology of acute anaphylaxis, as well as diagnostic tools available to diagnose it. We will also review appropriate interventions to save these emergent patients.

Anaphylaxis is defined in the Merriam-Webster dictionary as a “hypersensitivity resulting from sensitization following prior contact with the causative agent.” In other words, it is a hyper-response from the immune system to an allergen, food, or drug that the immune system has seen at least once before. In order to understand this reaction, it is key to learn the pathophysiologic mechanisms of the immune response, sensitization, and hypersensitivity.

IMMUNOLOGY BASICS
Immunoglobulins (also known as antibodies) are some of the primary components of the immune system. There are five classes of immunoglobulins (abbreviated “Ig”) that are common to all mammals: IgA, IgD, IgE, IgG, and IgM. These antibodies each have specific functions within the immune system and work together to create humoral immunity. IgA is found primarily in the mucosa of the gastrointestinal, urogenital, and respiratory tracts. IgD works against microbes in the bloodstream. IgG is the primary illness antibody, is found in extracellular fluid and the bloodstream and fights many pathogens by activating the complement cascade, stimulating further immune response. IgM precedes IgG in the bloodstream and acts as a stopgap until enough IgG can be produced. IgE is the primary immunoglobulin involved in the body’s response to allergens and parasitic infestations. It is also the antibody responsible for anaphylactic reactions.

An antigen is defined as any substance foreign to the body that evokes an immune response, or production of immunoglobulins. It can be a particle of pollen, a drug, a venom, a vaccine, a food, or a microbe. Antigens are detected by immune system components called T-cells. T-cells present antigens to B-cells, which are then stimulated to differentiate into plasma cells – antibody factories.

IgE is the antibody produced when antigens are first encountered by the immune system. In individuals without allergies or active parasite infestations, IgE is the least abundant antibody in circulation, comprising approximately 0.05% of all circulating antibodies. Individuals with allergies, conversely, have high levels of circulating IgE: their immune systems are primed for responding quickly to any antigen presented. IgE has a short half-life, as it is only required for immediate response to allergens. If the allergen or parasite persists, more IgE will be manufactured to respond to the continuing need.

HYPERSENSITIVITY REACTIONS
There are four traditional classifications of hypersensitivity reactions: Type IV are delayed-type reactions such as contact dermatitis and keratitis sicca. These reactions are triggered by antigen activation of helper T-cells which lead to the production of toxic macrophages and other cells that infiltrate tissues. Type III are termed “immune complex” reactions and include rheumatoid arthritis and serum sickness. Immune complexes are formed when an antibody binds to an antigen. These complexes can become embedded in tissues, leading to inflammation most commonly in the skin, joints, brain, lungs and kidneys. Type II are cytotoxic reactions mediated by IgG and IgM wherein the antibodies bind to antigens on a cell’s surface. These reactions include hemolytic reactions like IMHA as well as destruction of white blood cells and platelets. Type I reactions are also known as immediate or anaphylactic hypersensitivities. Type I reactions usually occur within 15-30 minutes of exposure to the antigen and are mediated by IgE. These reactions can be minor and localized – characterized by swelling, hives and
itching – more systemic – such as atopic dermatitis – or serious and systemic - as anaphylactic shock, or acute anaphylaxis.

ANAPHYLAXIS
As discussed above, IgE antibodies are produced when an antigen is first presented to the immune system. As the IgE antibodies circulate, they attach to basophils and mast cells throughout the body, arming these cells to respond quickly the next time the antigen is presented. When the antigen is reintroduced (as is the case with a second bee sting, or a repeat vaccination, or repeated ingestion of an antigenic food), it will bind to the IgE on the surface of the basophils and mast cells, leading to a cascade of degranulation of these cells and a release of their cellular contents into the bloodstream. The contents of these cells are potent inflammatory mediators, which lead to systemic reactions in the body.

One of the first mediators released is histamine, along with chemotactic factors. The chemotactic agents draw more immune cells to the area of degranulation, leading to further inflammation. There are four primary histamine receptors and each one contributes to the cascade of anaphylaxis. H₁ receptors are found in smooth muscle and endothelium and activation leads to cardiac depression, pruritus, vasodilation, bronchoconstriction, and vascular permeability. H₂ receptors are located in the gastrointestinal tract and endothelium and their activation causes tachycardia, inotropy, and systemic vasodilation. H₃ receptors are found on the myocardium and endothelium and their activation inhibits the effects of norepinephrine leading to decreased contractility and vasodilation. Finally, H₄ receptors augment further mediator release and increase chemotaxis, drawing inflammatory agents and other immune cells to the area of stimulation, increasing inflammation and stimulating the release of more inflammatory mediators. As you can see by comparing the effects of the different histamine receptors some have opposing effects (cardiac depression vs. inotropy) but the cumulative effect of stimulation of these receptors is systemic vasodilation, reduced cardiac output, and shock. To make matters worse, histamine also suppresses the effects of catecholamines like norepinephrine meaning that the compensatory mechanisms of the body are blocked, preventing vasoconstriction and a needed increase in cardiac output.

In addition to histamine, secondary inflammatory mediators are released such as heparin, platelet activating factor, interleukins, tumor necrosis factor, prostaglandins, and phospholipase A₂. These mediators induce platelet aggregation, activating the coagulation cascade, and cause continued vasodilation and increased vascular permeability. Permeable vessels leak vascular contents into interstitial spaces throughout the body leading to the phenomenon known as “third spacing” – a volume of fluid in the body that is not contributing to perfusion – worsening hypovolemia and profound hypotension. Increased vascular permeability in the larynx and the thorax leads to laryngeal and pulmonary edema. This edema, combined with bronchoconstriction from stimulation of histamine receptors, is a primary cause of death related to anaphylaxis. Those that do not succumb to asphyxiation are subject to the effects of distributive shock and – in human patients that do not seek treatment – death occurs in approximately one hour in up to 50% of those affected.

Clinical signs of anaphylaxis generally occur within one hour, but rapidity of onset is associated with more severe reactions. The site of antigen exposure determines the clinical signs exhibited. If the allergen is ingested, gastrointestinal distress and dermal reactions are most common. Inhaled allergens lead to a predominance of respiratory signs. The clinical signs most of us think of when we think of anaphylaxis are the most common: itching, hives, wheals, and redness. GI signs include hemorrhagic diarrhea and vomiting. Respiratory signs are those associated with bronchoconstriction and are manifested as sudden onset dyspnea. The inflammatory mediators also have direct effects on the myocardium, leading to arrhythmias. While there are similarities among species, cats and dogs are affected differently by anaphylaxis as a reflection of their organs that are most susceptible to shock. In dogs, the “shock organ” is the GI tract and the liver. On necropsy, dogs will often exhibit liver and visceral engorgement, with as much as 60% of their blood volume trapped in this “third space.” Cats’ (and most other mammals’)
primary “shock organ” is the lungs. Necropsies of anaphylactic cats often show signs of epiglottal edema, bronchoconstriction, and pulmonary hemorrhage.
Blood values for patients with acute anaphylactic reactions may be completely normal. Most commonly, patients present with an elevated hematocrit and high total protein levels. Pre-renal azotemia may be evident as a sequela of decreased renal perfusion. In dogs, liver enzyme elevation and prolonged clotting times may be noted though these changes usually aren’t evident until a few hours after presentation. Due to bronchoconstriction, most patients will have decreased oxygen levels in their blood, an academia, and hyperlactatemia.

Treatment of anaphylaxis must start with restoration of intravascular volume with boluses of crystalloid fluids. Fluids should be administered until normalization of blood pressure and other clinical signs. Epinephrine should be administered to counteract the vasodilatory effects of the inflammatory mediators and may need to be repeated until the desired response is seen. Administration of an antihistamine (usually diphenhydramine) can help resolve dermal signs. Adding an H₂ receptor blocker (such as famotidine) will help treat the gastrointestinal side effects of anaphylaxis by preventing the effects of histamine in the GI tract. Corticosteroids are often used in the treatment of acute anaphylaxis, though they take four – six hours to have an effect. Bronchodilators are a useful adjunctive treatment to help alleviate the dyspnea. Calcium blockers in particular (e.g. theophylline and aminophylline) are especially helpful as they increase endogenous epinephrine release and inhibit further histamine release. These agents can cause hypokalemia so their use should be monitored closely.

Goal-directed therapy is important to keep in mind when treating acute anaphylaxis. The resuscitation end-points include: a systolic blood pressure of 100-120mmHg; normalized urinary output; a PCV > 25%; a normal lactate (<2 mmol/L); normothermia; and improved levels of consciousness. As you can see, all of these goals can be achieved by restoring intravascular volume and perfusion.

A complete and thorough history from the client can help narrow down the cause of the anaphylactic reaction. If the reaction is related to a vaccination, the medical record should reflect the need for pre-medication prior to future vaccinations. If it appears that the reaction is related to a potential food allergy, a hydrolyzed protein diet trial should be conducted to find the antigenic protein so that it can be avoided in the future. In the case of reactions to bee stings, or envenomations, it is important for owners to know the severity of the reaction so that they can be prepared to act quickly in case of another exposure.

ANAPHYLACTOID REACTIONS
Anaphylactoid reactions present the same way as anaphylaxis, are not mediated by IgE. These reactions occur from exposure to things such as contrast media, NSAIDs, opioid administration, and exercise, among others. Because anaphylactoid reactions are not IgE mediated, a one-time exposure to an allergen can induce a reaction. These reactions are difficult to differentiate from anaphylaxis but, fortunately, treatment is the same.

CONCLUSION
While having an allergic reaction present to the clinic often seems like an “easy” case, these patients can quickly become complicated and deadly if not managed immediately and appropriately. Providing oxygen, IV fluid therapy, appropriate medications, and close monitoring can mean the difference between surviving an anaphylactic episode and not. Understanding the different causes and types of hypersensitivities is key to being able to educate clients on how to prevent allergic and anaphylactic responses in the future.

REFERENCES/SUGGESTED READING
Available upon request