Inviting Everyone to the Party: The Systemic Consequences of Anaphylaxis

Sarah Harris, CVT, VTS (ECC)

What is Anaphylaxis?:

Derived from Greek words *A (*against) & *phylaxis* (protection). A consensus of a uniformed definition of anaphylaxis had been challenging, despite distinct and rapid manifestation of clinical signs. Anaphylaxis is the acute onset of a systemic hypersensitivity reaction caused by the release of mediators from mast cells and basophils. Another way to say this is that anaphylaxis is a severe and potentially fatal systemic allergic reaction that occurs suddenly after contact with an allergen. A definitive set of criteria to diagnosis anaphylaxis vs. allergic reaction is somewhat lacking and likely contributes to misdiagnosis. A couple key differences in allergic reactions and anaphylaxis are the severity of the symptoms and the involvement of multiple organs and body systems. It is important to differentiate between the two clinical presentations as therapeutic approaches and interventions are not the same. We don't fully know the prevalence of anaphylaxis in small animal medicine, but we do know that it is happening more frequently. Patients are more frequently exposed to the antigens that cause this reaction both in the environment and in the therapies we provide in a clinic setting. While we do know some more frequent causes of anaphylaxis, it is important to know that any foreign substance can be a potential cause of anaphylaxis. It is nearly impossible to anticipate an anaphylactic reaction and the onset is very sudden, so a rapid diagnosis and treatment is essential to the outcome of the patient.

Types of Anaphylaxis:

Immunologic IgE mediated- patients have an initial exposure to an antigen in which they do not show clinical signs. When the patient is reexposed to the same antigen they produce IgE antibodies. These antibodies then bind to receptors in the membranes of mast cells and basophils which activate an d start the hypersensitivity reaction. Cell degranulation occurs leading to a rapid release of multiple mediators. These mediators interact with specific organs leading the onset of clinical signs.

Immunologic non-IgE mediated- still are immunologic in origin but occur through IgG antibody production. Antigen exposure activates the IgG antigen binding to receptors on macrophages. This type of reaction requires more antigen exposure and doesn't result in the release of the mediator histamine. Additionally, this type of reaction does not require the initial exposure to the antigen causing agent that is required in IgE type reactions.

Non immunologic reactions- in this type of reaction mast cell and basophils will degranulate with the involvement of IgE or IgG. External influences such as drugs, external toxins or other physical factors can trigger the event.

It is thought that most patients experience the first type of anaphylactic reaction (immunologic IgE mediated), but in a typical clinical setting it is very difficult to distinguish which type of anaphylaxis is

occurring. Regardless of the type, anaphylaxis can be life-threatening and therapeutic approaches to treatment are the same.

Chemical Mediators-
Mast Cells and Basophils store the chemical mediators that are responsible for the clinical signs seen in anaphylaxis. These mediators are released during degranulation that occurs after exposure to the inciting antigen. There is a long list of mediators including histamine, heparin, cytokines, prostaglandins, and platelet activating factor.

Histamine is the principal mediator of mast calls and basophils. During anaphylaxis it is very quickly released into circulation and elevated concentrations can be found less than 1 minute after interaction with inciting antigen. Histamine acts on receptors leading to signs of shock. Particularly, it is responsible for smooth muscle contraction which leads to vasodilation and subsequent decreased venous return, increased vascular permeability, increased gastric acid production. Additionally, it inhibits the release of exogenous norepinephrine which allows continued vasodilation and subsequent hypotension.

While histamine is often the most profound mediator. Other chemical mediators are also responsible for clinical signs seen in anaphylaxis and should be considered.

Heparin → hypocoagulable state, inhibits clot formation

Cytokines → increased cellular responsiveness to inflammatory mediators

Prostaglandins → bronchoconstriction, pulmonary/coronary vasoconstriction, peripheral vasodilation= airway obstruction, airway secretions, decreased cardiac output

Platelet activating factor → increased pulmonary resistance, decreased myocardial contractility, vasodilation, hypotension and platelet aggregation (thrombus formation). Decreased myocardial contractility + vasodilation= profound hypotension.

Anaphylactic shock and the shock organs of dogs and cats:

Shock simply put is the inadequate delivery of oxygen to tissues and the decreased cellular energy production. Anaphylactic shock is a type of distributive shock and is the result of the massive vasodilation secondary to mast cell degranulation, histamine release, and the rapid release of inflammatory and vasoactive mediators mentioned. Vasodilation in turn decreases the relative circulatory volume, decreasing perfusion and thus oxygen delivery to tissues. This leads to splenic contraction and tachycardia, and ultimately myocardial and cerebral hypoxemia, cardiovascular collapse, and death.

The target organs of anaphylaxis are dependent on the location and concentration of mast cells within the body. In dogs, the target organ is the gastrointestinal tract, especially the liver. In cats, the target organ is the respiratory tract. Species differences in the location of mast cells contributes to the clinical signs in patients with anaphylaxis. For this reason, dogs with anaphylaxis are much more likely to have vomiting and diarrhea which may progress to hemorrhagic diarrhea. Cats are much more likely to present with collapse and respiratory distress. While dogs are much less likely to develop respiratory signs, it can be seen more commonly in brachycephalic breeds who are less capable of compensating for facial or laryngeal edema.

Causes of anaphylaxis:

Any foreign substance can be a potential cause of anaphylaxis, but there are some recurring antigens that are more frequent anaphylactic causing agents.

Hymenoptera- Hymenoptera is an order of insects including bees, wasps, hornets and ants. Each one of these insects has a slightly different effect in patients. Bees One sting (barbed stinger)

- *Bees*-
    - Contain a mast cell- degranulating peptide
    - Histamine release
    - Catecholamine release
    - Changes to cell permeability (potassium shifts extracellularly)
    - Intravascular hemolysis
- *Wasps/Hornets*-
    - Multiple stings (smooth stingers & aggressive)
    - Hornet cause more painful stings because of acetylcholine in venom
    - Mostly proteins as bee venom
    - May produce a toxic envenomation response
    - Estimated lethal dose is 20 stings/kg
- *Fire Ants*-
    - Multiple stings (attach with mandibles, non-barbed stinger, very aggressive)
    - Alkaloid venom causes cytotoxic hemolytic pustules
    - Anaphylactoid response (does not elicit an IgE-mediated response)

Medications

Any medication has the potential to be an inciting cause for anaphylaxis. Some of the more common medications include ophthalmic antibiotic ointments in cats, chemotherapy agents, contrast material used in imaging and a variety of injectable medications.

Blood Transfusions-
Patients receiving blood transfusion have the potential to have IgE-mediated anaphylactic reactions because of the presence of IgE and mast cells. Clinical signs reported range from mild to life-threatening. Diligent monitoring for both allergic and anaphylactic reactions should be performed both throughout and after the administration of blood products. Delayed reactions have been documented.
Systemic consequences of anaphylaxis-

Integumentary- cutaneous clinical signs are more likely to be found secondary to an allergic reaction than anaphylaxis. However, cutaneous signs could be a precursor to a delayed onset of anaphylaxis in some patients. Typically, these signs are absent with the acute onset of anaphylaxis or much more subtle and short lived than they are with allergic reactions. They are also more likely to develop in dogs than cats. The most common clinical signs include urticaria, erythema, pruritus and angioedema.

Respiratory- signs can occur in both dogs and cats. The respiratory tract is the target organ in cats because of the increased concentration of mast cells in the respiratory tract of cats. Therefore, cats are more likely to present with collapse, tachypnea, dyspnea, and hypoxemia than dogs. Signs may also include laryngeal and pharyngeal edema, bronchoconstriction, increased mucus secretion, bronchospasm, stridor and coughing. Clinical signs may be exaggerated in brachycephalic breeds.

Cardiovascular- Profound vasodilation is a major consequence of anaphylactic shock and this can lead to life threatening hypotension if interventions and treatments are not rapidly initiated. Chemical mediators also lead to increased vascular permeability that can lead to rapid, substantial decreases in intravascular blood volume. Clinical signs related to the cardiovascular system are often the most tell-tale signs of anaphylaxis. Clinical signs may include tachycardia, cardiac arrhythmias, pale or brick red mucous membranes, prolonged capillary refill time, poor pulse quality, cold extremities, hypothermia and a dull or depressed mentation.

Gastrointestinal- with the target organ of anaphylaxis in dogs being the gastrointestinal tract, clinical reactions are commonly seen. Mast cell location and degranulation lead to histamine released from the gastrointestinal tract to be released into the portal vein which leads to hepatic venous congestion and portal hypertension. Clinical signs may include vomiting and diarrhea that may or may not become hemorrhagic. While gastrointestinal clinical signs are more common in dogs, they also may occur in cats. And while anaphylaxis is usually considered a clinical diagnosis with laboratory tests being of little value, the attack on the gastrointestinal tract can lead to some key diagnostic markers. The pathophysiologic changes often lead to an elevated alanine aminotransferase (ALT). This can be seen in the first 12 hours with peak elevations occurring between 24-48 hours after onset of clinical manifestation. The other diagnostic marker is detectable on ultrasound evaluation of the gallbladder. Anaphylaxis can cause near immediate inflammation which leads to striations in the wall of the gallbladder creating the telltale “halo effect” seen on ultrasound.
Pharmaceutical and Therapeutic interventions:

Treatment for anaphylaxis must be initiated quickly and should always be prioritized over diagnostics. If treatment is not started, clinical signs will continue to rapidly progress and may lead to death. Treatment for anaphylaxis is highly dependent on clinical presentation and should include fundamental life support interventions. It does not matter if the anaphylactic reaction is immunologic or nonimmunologic because clinical signs and therapeutic recommendations are the same. What is important is that delays in treatments may lead to worsening outcomes. Pharmaceutical interventions are essential to successful treatments of anaphylaxis, with epinephrine being key in severe cases. Other common pharmaceuticals include antihistamines, glucocorticoids, and bronchodilators. In severe cases, more aggressive approaches may be needed and may include vasopressors and anticholinergics.

Therapeutic inventions are also essential and initial aggressive stabilization is required. Obtaining vascular access is key and can be challenge in patients with vascular collapse. A short, large bore IV catheter will best facilitate the initial fluid boluses that are likely needed for treatment of hypotension and hypovolemia. Fluid therapy is a mainstay therapy that is needed to address that anaphylactic patient who is hemodynamically unstable. Volume resuscitation is patient dependent and should be tailored to their responsiveness. Adequate resuscitation should be based on perfusion parameters such as mentation, mucous membrane color, capillary refill time, blood pressure and blood lactate measurements. Other initial therapies should include oxygen therapy with benefits both the respiratory and hemodynamically compromised patient. Oxygen can be administered via face mask, nasal cannulas or catheters, oxygen cage, or endotracheal tube depending on the patient's specific need.
Nursing care and hospitalization:

It is important to know that anaphylaxis can have a biphasic presentation. This is seen by the resolution of clinical signs only for them to reappear again hours to days after they resolve. For this reason, hospitalization and monitoring is usually required for 48-72 hours after anaphylaxis occurs. Nursing care is patient dependent but likely will require diligent monitoring of perfusion parameters until stabilized. Once stabilized, nursing care shifts to monitoring for fecal scalding secondary to ongoing gastroenteritis, monitoring all body systems for the return of clinical signs, the administration of ongoing pharmaceuticals and providing much needed TLC for the patient recovering.

References:

Aharon, M. A., Prittie, J. E., & Buriko, K. (2017). A review of associated controversies surrounding glucocorticoid use in veterinary emergency and critical care. *Journal of veterinary emergency and critical care (San Antonio, Tex. : 2001)*, *27*(3), 267–277. https://doi.org/10.1111/vec.12603

Bracker, K. E., & Drellich, S. (2005). Transfusion Reactions. *Emergency Medicine Compendium*, *7*(7). Retrieved from https://www.vetfolio.com/learn/article/transfusion-reactions

Caldwell, D. J., Petras, K. E., Mattison, B. L., Wells, R. J., & Heffelman, V. L. (2018). Spontaneous hemoperitoneum and anaphylactic shock associated with Hymenoptera envenomation in a dog. *Journal of veterinary emergency and critical care (San Antonio, Tex. : 2001)*, *28*(5), 476–482. https://doi.org/10.1111/vec.12751

Flores, R., & Thawley, V. (2019). Hymenoptera Envenomation. In *Textbook of Small Animal Emergency Medicine, I&II* (pp. 930–935). John Wiley & Sons, Inc. https://doi-org.libproxy.pcc.edu/10.1002/9781119028994.ch145

Herold, L. (n.d.). Anaphylaxis Q & A. Retrieved from https://www.atdove.org/article/anaphylaxis-q

Hume-Smith, K. M., Groth, A. D., Rishniw, M., Walter-Grimm, L. A., Plunkett, S. J., & Maggs, D. J. (2011). Anaphylactic events observed within 4 h of ocular application of an antibiotic-containing ophthalmic preparation: 61 cats (1993-2010). *Journal of feline medicine and surgery*, *13*(10), 744–751. https://doi.org/10.1016/j.jfms.2011.06.007

Lyons, J. L., & Scherk, J. R. (2017, July/August). Anaphylactic Shock: How to Effectively Diagnose and Treat. Retrieved from https://todaysveterinarypractice.com/anaphylactic-shock-effectively-diagnose-treat/

Plunkett, S.J. (2000), Anaphylaxis to Ophthalmic Medication in a Cat. *Journal of veterinary emergency and critical care*, 10: 169-171. https://doi.org10.1111/j.1476-4431.2000.tb00007.x

Quantz, J. E., Miles, M. S., Reed, A. L., & White, G. A. (2009). Elevation of alanine transaminase and gallbladder wall abnormalities as biomarkers of anaphylaxis in canine hypersensitivity patients. *Journal of veterinary emergency and critical care (San Antonio, Tex. : 2001)*, *19*(6), 536–544. https://doi.org/10.1111/j.1476-4431.2009.00474.x

Smarick, S. (2019). Additional Mechanisms of Shock. In *Textbook of Small Animal Emergency Medicine, I&II* (pp. 1000–1004). John Wiley & Sons, Inc. https://doi-org.libproxy.pcc.edu/10.1002/9781119028994.ch155