Anaphylaxis: pathophysiology, therapy and prognosis

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Anaphylaxis is a severe systemic and potentially fatal hypersensitivity reaction which can occur secondary to a wide variety of antigens. It can be triggered through immunologic means - stimulation of IgE receptors in a type I hypersensitivity or, less commonly through stimulation of IgG receptors in the non-IgE mediated pathway. Non-immunologic stimulation of anaphylaxis due to extreme temperature or exercise have also been reported. The clinical manifestations associated with anaphylaxis depend on the species affected, the type of stimulation and the "shock organs" of that species.

Pathoaetiology

The classic immune mediated mechanism of anaphylaxis is through an IgE mediated event requiring initial sensitization to an antigen (Figure 1). The subsequent IgE antibodies bind to the membranes of tissue mast cells and circulating basophils. Upon re-exposure, the same antigen binds and cross links the IgE antibodies – resulting in intracellular secondary messenger systems and release of preformed vasoactive and inflammatory mediators and synthesis of additional mediators. As these effector cells are disseminated throughout the body, the response is much more rapid and potent than the initial response.

Activation of the immune cells, particularly mast cells, basophils and neutrophils, results in release of numerous peptides, cytokines and hormones (Table 1) that result in the clinically noted manifestations of anaphylaxis. Vasoactive and pro-inflammatory mediators such as histamine, tryptase, heparin and cytokines (prostaglandins, bradykinin, prostacyclin, leukotrienes and thromboxane A2) all ultimately result in the constellation of clinical signs associated with anaphylaxis (Table 1).

These mediators result in smooth muscle contraction, vasodilation and increased vascular permeability. There is also risk of development of disseminated intravascular coagulation, and multiorgan dysregulation. In some cases, there is significant development of hypocoagulability/coagulopathy secondary to a combination of consumptive coagulopathy and release of endogenous heparins.

Diagnosis

Diagnosis of anaphylaxis can be challenging due to the lack of readily available definitive diagnostic test. It is generally based upon history, recognition of clinical signs and physical exam findings. Clinical criteria for diagnosis are utilised in human medicine, however these have not been conclusively established in veterinary species. Generally accepted diagnostic criteria for anaphylaxis in dogs and cats are shown in Figure 2. Elevation of ALT in a canine patient with consistent clinical signs should increase index of suspicion of anaphylaxis (85%

sensitivity and 98% specificity in one study). Point of care ultrasonography demonstrates gall bladder wall oedema or "halo" sign with 93% sensitivity and 98% specificity. Abdominal effusion (haemoabdomen), evidence of coagulopathy, DIC, liver dysfunction and secondary MODS can all be seen in more severe anaphylactic exams

Treatment

"In veterinary medicine, no randomized controlled trials have been performed to evaluate the medications most commonly used in the treatment of anaphylaxis and the choice of treatment therefore remains controversial."- Textbook of Small Animal Emergency Medicine, Ch 146, pp 939, Drobatz et al.

Required treatment is largely dependent on severity of clinical signs. Emergency treatment should be initiated in all patients in which there is reasonable clinical suspicion for anaphylaxis, due to the risk of rapid and severe deterioration. Adrenaline (aka epinephrine in the USA) is considered the mainstay of anaphylaxis therapy, through its vasoconstrictive and positive inotropic and chronotropic effects. Administration IV as a CRI is preferred, although IM is appropriate if vascular access has not been yet attained (Doses in Table 2). IV fluid therapy is also important if the patient has significant hypovolaemia due to gastrointestinal losses and third spacing into the abdomen, which is commonly encountered in the canine patient. Antihistamines are commonly used in veterinary medicine to treat hypersensitivity reactions. H1 antihistamines have been shown to reduce pruritus associated with antigenic exposure, however, they have not been shown to be effective in alleviating the cardiovascular effects of anaphylaxis. Antihistamines can be used as an ancillary treatment for the urticaria and pruritus commonly encountered in anaphylaxis; but should not be substitute for adrenaline and crystalloid therapy. Glucocorticoids are also commonly utilised in veterinary medicine to treat hypersensitivity, however there is no evidence to support or refute their use in anaphylaxis. It is important to remember that the onset of action of glucocorticoids is several hours, and therefore has minimal benefit in the acute phase of this presentation. The use of Beta-2 agonists or methylxanthines may be useful to assist in respiratory signs associated with anaphylaxis, particularly in cats, or dogs who have been stung adjacent to their airways. In a subset of animals, there will be significant hypocoagulability and bleeding diathesis due to a combination of systemic heparinisation and consumptive coagulopathy. In these animals' administration of fresh frozen plasma may be required to normalise coagulation and provide oncotic support in the actively bleeding patient. Additional therapy to support gastric mucosal health with proton pump inhibitors is reasonable in this patient cohort. Supportive care of any organ system which develops dysfunction is essential as with any critically ill patient.

Prevention

As hymenoptera envenomation is the most common allergen associated with anaphylaxis in the canine population, the use of venom immunotherapy (VIT) has been an area of active research. In humans, VIT has an efficacy of up to 98% in preventing further anaphylactic/severe reactions. There is a moderate amount of information regarding the various protocols and risk of side effects in VIT in the veterinary literature, primarily

produced by dermatologists as they are most comfortable in administering immunotherapeutic protocols. There is a moderate risk of low grade localised reaction during therapy, and low risk of systemic reactions. There is very limited data on the lasting clinical efficacy of VIT, however, a 2023 paper by Rostaher et al found that only 1/7 dogs who were re-exposed (stung) following VIT had any reaction, and this was limited to local angioedema, rather than the severe anaphylaxis noted prior to VIT.

It is also important to try and identify a trigger, in an effort to reduce the risk of repeat exposure, and potentially as a preventative treatment target through VIT.

The use of at home adrenaline or Epi-pen auto-injectors is controversial due to the difficulty of accurately dosing, and shortness of the human-designed needles preventing effective IM administration in many cases. The non-specific clinical signs associated with anaphylaxis (GI upset and collapse), may also cause owners to administer adrenaline due to other causes of unwellness where it is not clinically indicated and may have negative side effects (hypertension, tachyarrhythmias, splanchnic vasoconstriction).

Prognosis

The prognosis associated with anaphylaxis is largely dependent on the severity of clinical signs associated with each presentation. In a 2020 retrospective evaluation of mortality and prognostic indicators by Smith et al, the overall mortality was 14.9%, however it should be noted that this cohort was specifically selected for “severe anaphylaxis”. Prognostic markers associated with increased mortality were elevations in serum phosphorous (>12mmol/L), lower presenting body temperature, hypoglycaemia within 6 hours post admission, elevated prothrombin time and concurrent elevation in prothrombin and partial thromboplastin times >50% above baseline. There was also noted to be high incidence of coagulopathy (85.2%) and peritoneal effusion (65.5%) however these were not predictive of mortality.

Conclusions

In conclusion anaphylaxis describes a poorly defined spectrum of disease states of varying severities that occur secondary to an exogenous trigger. In the most severe cases this can a rapidly progressive and fatal syndrome requiring prompt and aggressive therapy.

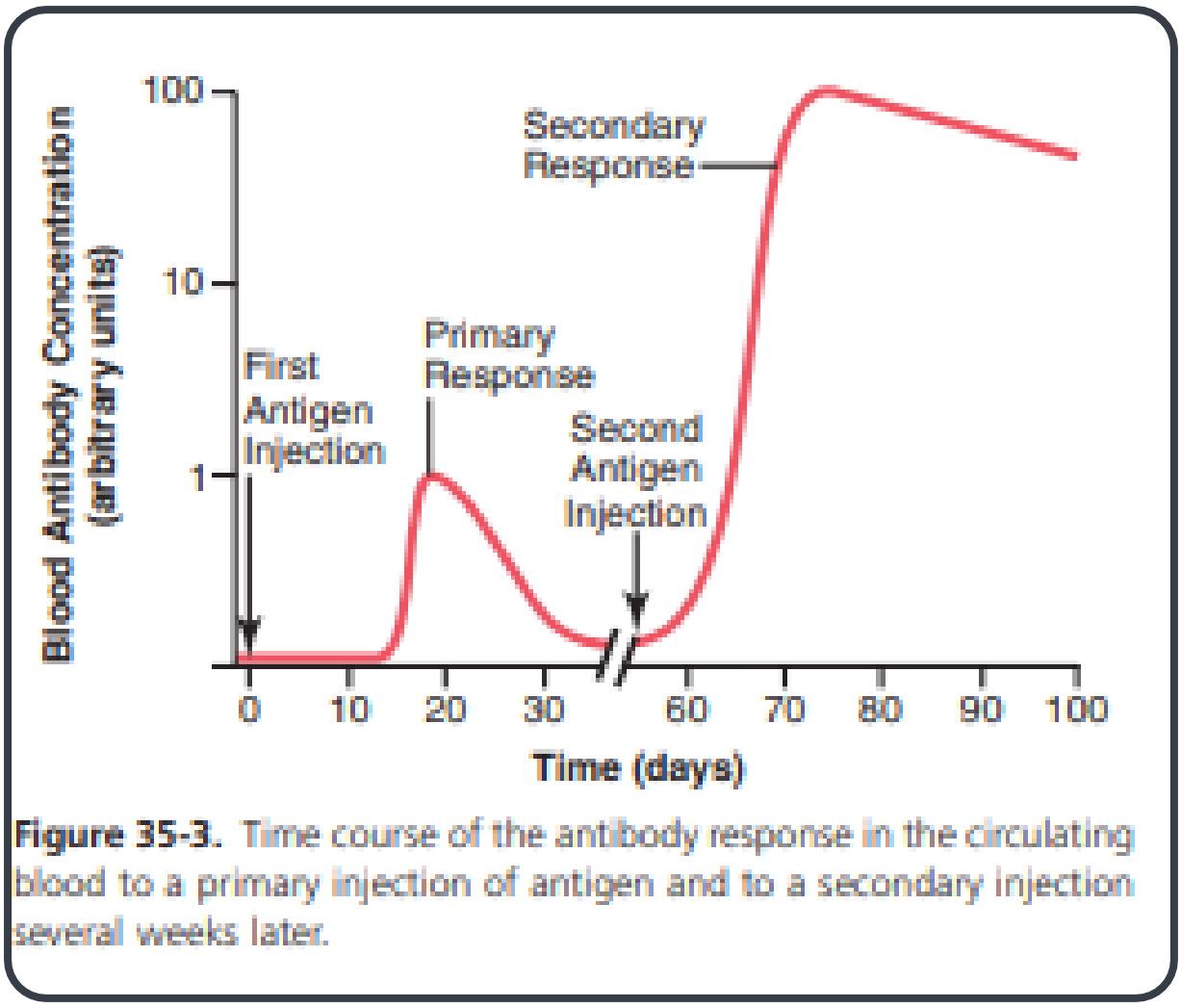

Figure 35-3. Time course of the antibody response in the circulating blood to a primary injection of antigen and to a secondary injection several weeks later.

Figure 1. Highlighting the difference in immune response speed and severity in an initial vs second exposure. *Adapted from Guyton and Hall – Chapter 35 – resistance of the body to infection – immunity and allergy pp - 469*

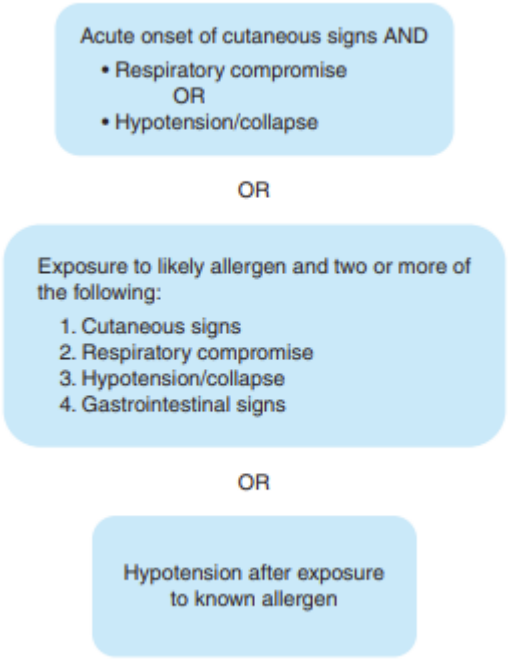

Fig. 141.3 Diagnostic criteria for anaphylaxis in dogs and cats.

Figure 2. Proposed diagnostic criteria for anaphylaxis in dogs and cats. *Adapted from Small Animal Critical Care Medicine, 3rd Ed. – Ch141 – Anaphylaxis pp 828*

Table 1: Mediators associated with Anaphylaxis

Primary Mediators	
Mediator	**Primary Effect in anaphylaxis**
Histamine	- Vasodilation - Increased vascular permeability - Increases NO production – more vasodilation – coronary and systemic - Stimulates gastric acid secretion - Inhibition of endogenous noradrenaline
Proteases - Tryptase - Chymase - Carboxypeptidase A3	- Junctional protein degradation – increased permeability - Exact mechanism is incompletely known
Heparin	Potent anticoagulant, opposes complement activation
Eosinophil Chemotactic Factor-A	Attracts Eosinophils and results in greater secondary degranulation and release of cytokines and secondary mediators

Neutrophil Chemotactic Factor-A	Attracts Neutrophile and results in greater secondary release of cytokines and secondary mediators
Secondary Mediators	
Mediator	**Primary Effect in anaphylaxis**
Prostaglandins E2 and D2	- Arachidonic acid metabolites – local and systemic vasodilation, increase WBC recruitment and activation - Bronchoconstriction - Pulmonary and coronary artery vasoconstrictors - Peripheral vasodilators
Bradykinin	- Potent vasodilator - Activates Factor Xii – contributes clot formation + consumptive coagulopathy - Activates plasmin -> fibrinolysis
Prostacyclin (PGI-2)	- Vasodilator - Anti-platelet aggregatory effect - Possible modulatory role and protective against inflammatory response
Leukotrienes - LTC4 - LTD4 - LTE4	Collectively known as - Slow-reactive substance of anaphylaxis (SRS-A) – a potent bronchoconstrictor, works slower than the above mediators, but has greater potency
Thromboxane A2	- Procoagulant – platelet activation and increased aggregation. - Vasoconstrictor
Platelet activating Factor	More important in non-traditional pathway (IgG mediated). Causes bronchoconstriction and peripheral vasodilation
Complement system activation - Particularly C3a	- C3a – aka anaphylaxotoxin – further increases mast cell and basophil degranulation - increased vascular permeability - increased smooth muscular contracture – bronchoconstriction and vasodilation
Cytokines	
Mediator	**Primary Effect in anaphylaxis**
IL-1 & Tumour Necrosis Factor - α (TNF-α)	- Proinflammatory mediators - Increased expression adhesion molecules on venular endothelia
IL-4 & IL-13	Increased IgE production

- IL-3 - IL-5 - IL-6 - IL10 - Transforming Growth Factor – β (TGF-β) - Granulocyte/Macrophage – Colony Stimulating Factor (GM-CSF)	Multiple effects - Upregulate production of granulocytes and macrophages - Icnrease T and B cell maturation and differentiation - Some anti-inflammatory effects primarily from IL-6, IL-10 and TGF-β

Table 2: Suggested Treatment drugs and Doses for anaphylaxis

Treatment	**Details, dose and route**
IV isotonic balanced crystalloid bolus administration (LRS, Hartmanns, Plasmalyte or Normosol R recommended over 0.9% NaCl)	As indicated for hypovolaemia, with ongoing fluid administration dependent on losses and requirements - Dogs 10-20ml/kg bolus over 15 minutes then re-evaluate - Cats 5-10ml/kg bolus over 15 minutes then re-evaluate
Adrenaline (epinephrine)	0.01-0.025mg/kg IM or IV 0.05µg/kg/min CRI
Diphenhydramine	Dogs - 1-4mg/kg IM or IV Cats – 0.5-2mg/kg IM or IV
Dexamethasone – anti-inflammatory dosage	Not indicated for primary treatment of acute anaphylaxis 0.1-0.15mg/kg (1mg/kg prednisone equivalent)
Bronchodilator therapy	As required for airway swelling, more likely to be required in cats - Albuterol/salbutamol 1-2 puffs of 90µg inhaler or 0.5mL of 0.5% solution in 4mL 0.9% NaCl nebulization - Terbutaline 0.01mg/kg IM or IV - Aminophylline 5-10mg/kg IM or IV
Other supportive care - Oxygen therapy - Antinausea - Antacids	- Oxygen therapy should be considered in all patients until stabilised, ongoing if respiratory compromise - Maropitant 1mg/kg IV - Ondansetron 0.5mg/kg IV Q8 PRN - Esomeprazole/pantoprazole 1mg/kg IV Q12

Coagulopathy therapy - Fresh Frozen plasma	- If hypocoagulable and evidence of active/ongoing haemorrhage – give FFP 10ml/kg – then reassess – can be repeated for 20ml/kg total dose - FWB or pRBC transfusions as required for red cell replacement if haemorrhage is severe

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