ANAPHYLAXIS IN SMALL ANIMALS

Julia Almenta Serrato, DVM, Small Animals Rotating Intern, University College Dublin (under the guidance of Cormac Dolan, MVB, Dip ECVECC), provides an overview of anaphylaxis in small animals. This article presents a comprehensive review of anaphylaxis in small animals, focusing on clinical presentation, diagnostic strategies, and treatment options. Additionally, two case reports illustrate the clinical approach and outcomes related to this condition

There is currently no consensus regarding the definition of anaphylaxis in small animals. A recent report in human medicine defines anaphylaxis as 'a serious allergic (hypersensitivity) reaction that can progress rapidly and may cause death. Previous nomenclature included anaphylactic (IgE-mediated) and anaphylactoid (non-IgE-mediated) reactions; however, the latter term has fallen out of favour.

Currently, anaphylactic reactions are classified as:

1. Immunologic IgE-mediated: Causes may include insect stings or bites, snake envenomation, food, and drugs such as β-lactam antimicrobials, among others.
2. Immunologic non-IgE-mediated: Causes may include immune aggregates (e.g., IV immunoglobulin, such as IgG- or IgM-related, transfusions), complement system activation, coagulation system activation, and autoimmune mechanisms.
3. Non-immunologic: Causes may include physical factors (e.g., heat or cold exposure, water, and exercise) and certain medications. These factors directly stimulate mast cells, and therefore, previous exposure (sensitisation) is not required.

Despite this nomenclature, all mechanisms result in immune cell activation. The most commonly reported causes of anaphylaxis in dogs include Hymenoptera (bee, wasp, ant) venom, vaccines, and drugs. Previous retrospective studies document Hymenoptera envenomation as a cause for approximately half of the cases of anaphylaxis. This type of hypersensitivity reaction (type I) is initiated by antigen sensitisation, during which exposure to an allergen induces production of IgE antibodies that bind to high-affinity FcεRI receptors on mast cells and basophils. This sensitisation phase is clinically silent. Upon re-exposure, the allergen cross-links adjacent IgE molecules on the mast cell surface, triggering intracellular signalling with calcium influx and subsequent mast cell degranulation. This results in the rapid release of preformed mediators such as histamine, tryptase, chymase, and heparin, along with other mediators including serotonin (see Figure 1).

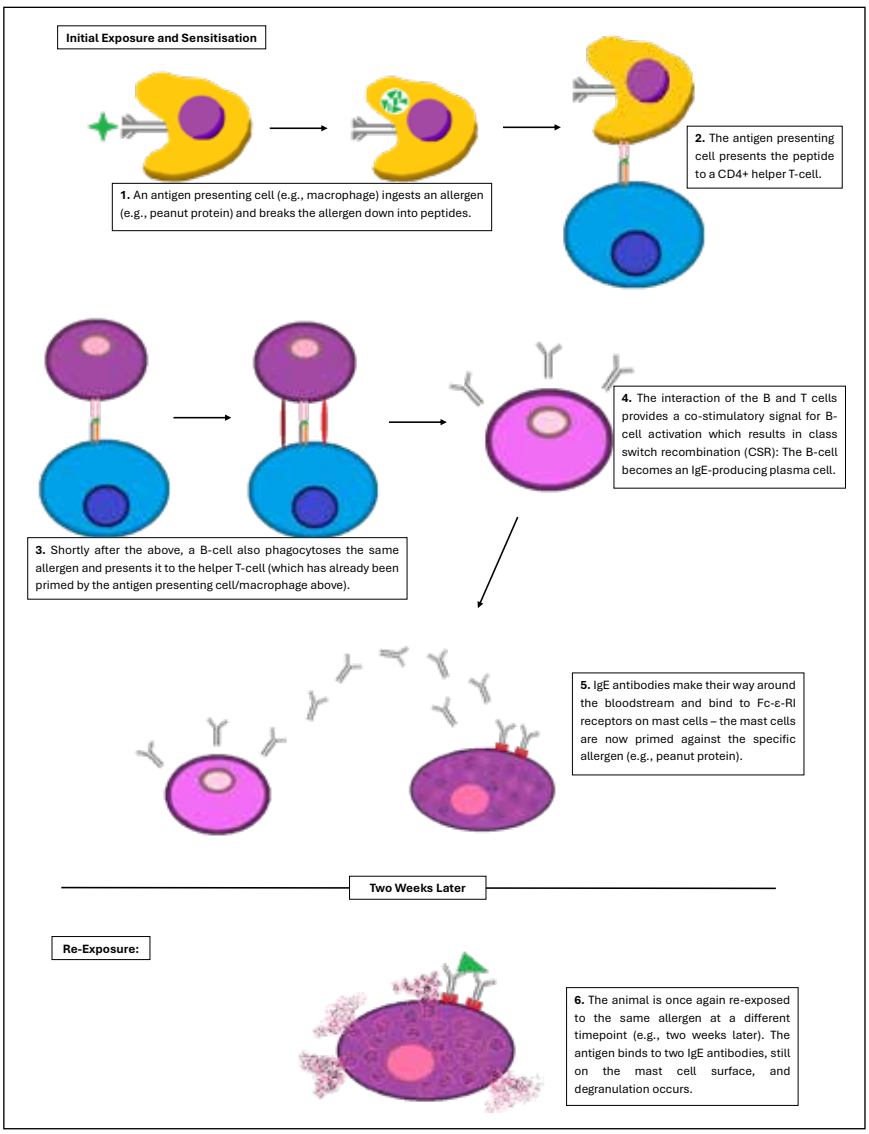


Figure 1: Mechanism of anaphylaxis.

In addition, newly synthesised mediators are generated, notably platelet-activating factor (PAF) and lipid-derived compounds. Mast cell activation also induces the production of cytokines, including TNF-α, IL-4, IL-5 and IL-13, which amplify and sustain the inflammatory response. Histamine further promotes vasodilation partly through induction of nitric oxide production.

Together, these mediators lead to increased vascular permeability, vasodilation, bronchoconstriction and recruitment of inflammatory cells, ultimately producing the systemic clinical manifestations of anaphylaxis.

In their most severe forms, systemic immune cell activation can result in circulatory collapse, known as anaphylactic

shock, a type of distributive shock, whereby marked vasodilation and inappropriate congestion in certain vascular beds ensues, resulting in a state of relative hypovolaemia and reduced venous return. Fluid extravasation and gastrointestinal losses can contribute to true hypovolaemia and direct myocardial depression can also occur. Pulmonary vasospasm can occur and may introduce a component of obstructive shock by reducing left ventricular filling. Maldistribution of vascular volume results in altered blood flow to specific organ systems; in dogs, it primarily affects the gastrointestinal tract and liver, whereas the respiratory tract is most commonly affected in cats, and the lungs and heart are mainly affected in humans.

Clinical signs

Clinical manifestations of anaphylactic reactions are therefore species-dependent and reflect which major organ systems are affected. These differences are influenced by variations in immune response, the distribution of smooth muscle, the rate of antigen degradation, and the responsiveness to inflammatory mediators. They are also directly related to the location of the largest population of mast cells.

The signs usually occur within minutes of antigenic exposure although occasionally some reactions may not develop for hours. Generally, the onset of clinical signs correlates with the severity of the systemic reaction, such that earlier manifestation following antigen exposure is associated with greater severity. In dogs, the severity of shock appears to be proportional to the degree of hepatic and gallbladder congestion.

The clinical signs can be divided into four major categories: cutaneous, respiratory, cardiovascular, and gastrointestinal. Cutaneous signs, such as generalised erythema, urticaria, pruritus, and facial angioedema, are generally considered early indicators of more severe anaphylactic reactions; however, profound cardiovascular collapse and shock may occur in the absence of any cutaneous manifestations. It is very important to acknowledge that cutaneous signs can be challenging to identify, as they may be obscured by fur and pigmentation.

Respiratory signs are among the most frequent signs reported in cats. Respiratory signs may include: open-mouthed breathing, respiratory distress, tachypnoea, stridor and cough. These signs are often as a result of laryngeal and pharyngeal oedema, excessive mucus production and bronchospasm.

Cardiovascular compromise during anaphylaxis is primarily characterised by hypotension, associated vasodilation, and fluid extravasation, leading to a mixed distributive-hypovolemic shock pattern. The redistribution of blood volume can result in a rapid, haemodynamic collapse. In response to this decreased effective vascular volume, a compensatory tachycardia is frequently noted. However, bradycardia can also occur, possible explanations for which include neurocardiogenic mechanisms and the effect of anaphylactic mediators on the nervous system and myocardium. Since patients can present with mixed shock patterns, mucous membranes may be injected or pale, capillary refill time can be rapid or prolonged, and pulse quality may be weak or hyperdynamic. Other cardiovascular signs may include arrhythmias, myocardial ischemia, and cardiac arrest.

Hepatic and gastrointestinal signs are also very frequent; hepatic arterial vasodilation in combination with hepatic venous outflow obstruction generates significant portal hypertension and visceral pooling of blood leading to vomiting and diarrhoea. Consequently, immediate and fulminating haematochezia is one of the main clinical signs in dogs. Gastrointestinal signs are also frequently observed in cats with one retrospective study reporting vomiting in 69 per cent of cases.

Other manifestations of an anaphylactic reaction include neurologic and ocular signs, such as weakness, syncope, seizures, conjunctivitis and lacrimation.

Diagnosis

Due to the wide variability in clinical manifestations, anaphylactic reactions can be difficult to diagnose. Therefore, diagnosis relies primarily on clinical history and pattern recognition. This includes the acute onset of characteristic signs following exposure to a known or potential trigger, the time interval between exposure and onset of clinical signs, and the progression of these manifestations. A diagnostic aid has been proposed in dogs and cats (see Figure 2).

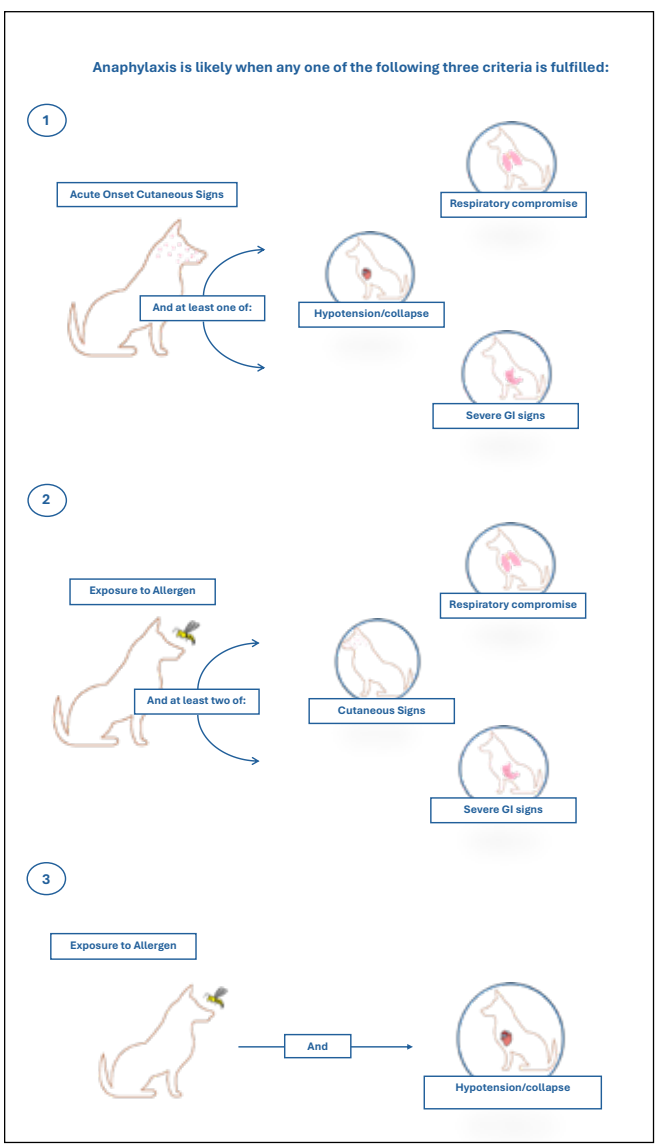


Figure 2: Diagnostic aid for canine anaphylaxis.

Even if it is considered a non-specific finding, thickening of the gallbladder may be seen on ultrasound. Multiple striations within the wall and the double rim effect are indicative of wall oedema or inflammation and can be associated with causes unrelated to gallbladder disease. With hepatic venous congestion and portal hypertension in canine anaphylaxis, venous drainage of the gallbladder is impaired, and similar changes of the gallbladder wall are expected. In one retrospective study, the double rim sign was identified in 93 per cent of dogs with anaphylaxis. This same hepatic venous outflow block is suspected to be the cause of an increase in ALT activity. A canine patient presenting with acute-onset hypotension or gastrointestinal signs, together with an isolated increase in ALT activity or gallbladder wall oedema, or both, should prompt strong consideration of anaphylaxis as a differential diagnosis.

Dogs with anaphylaxis have also been reported to develop spontaneous peritoneal effusion, particularly haemoperitoneum, as with Case 1 below. The exact pathophysiology remains unclear and is likely multifactorial. It may be due to the marked increase in hepatic venous pressure along with histamine-induced increased vascular permeability. Other causes may be due to mast cell release of heparin, or other mediators, resulting in hypocoagulability.

Many biomarkers have been evaluated in both human and veterinary medicine. In human medicine, both histamine and total tryptase concentrations have been shown to support the diagnosis of anaphylaxis. In canine patients, increased histamine concentrations and a normal C-reactive protein (CRP) may have a role in discriminating anaphylaxis from other illnesses in the acute period. The differential diagnoses for anaphylaxis include severe asthma, septic shock, hypovolaemic shock, acute gastrointestinal diseases, vasovagal events, and systemic mastocytosis.

Treatment

Like in most emergencies, treatment begins with a rapid assessment of airway, breathing, circulation, and mental status. Aggressive treatment should be initiated prior to diagnostics due to the rapid deterioration and mortality that may occur. However, the treatment of anaphylaxis is subjective and should be individualised on a case-by-case basis, being tailored to the type and severity of clinical signs.

Adrenaline is an essential drug in the management of anaphylaxis. Through its α-adrenergic activity, adrenaline mitigates the vasodilatory effects of histamine. The α-adrenergic effects also decrease mucosal oedema within the airways. Stimulation of β-adrenergic receptors results in increased myocardial contractility, improving cardiac output, as well as causing bronchodilation. Importantly, β-adrenergic activity results in stabilisation of mast cells and basophils, preventing further degranulation.

Interestingly, numerous studies have shown no beneficial effects and even deleterious effects of adrenaline once patients show signs of circulatory shock. Evidence points towards continuous infusions of adrenaline being superior to bolus therapy and that early administration, even prior to antigen exposure, may improve outcomes.

While prospective studies are needed, the early administration of adrenaline in patients presenting with apparently stable, but evolving, type I hypersensitivity reactions may improve outcomes in the subcategory of patients that subsequently develop fulminant anaphylaxis. Despite this, multiple retrospective studies have reported high survival rates (91.8 per cent-100 per cent) in canine anaphylaxis cases, even in the absence of early adrenaline administration. In the clinical setting, the authors normally administer a bolus of 0.01 mg/kg intramuscularly followed by a continuous infusion of 0.05μg/kg/minute with continuous electrocardiogram monitoring. The rate of the continuous infusion can then be tailored to the patient's requirements. As a general rule, the rate can be increased quickly at 0.05μg/kg/minute increments up to a maximum of 1μg/kg/minute. Once the patient is haemodynamically stable, the dose can be more slowly tapered.

Although adrenaline is widely regarded as the first-line treatment for anaphylaxis, the authors propose that intravenous fluid therapy may represent the more critical initial intervention, as the administration of adrenaline in the face of true hypovolaemia secondary to cavitary and gastrointestinal third spacing is unlikely to be effective and may even be deleterious. Furthermore, retrospective studies have shown good outcomes with fluid therapy alone. Aggressive fluid resuscitation is normally recommended, particularly in hypotensive patients. One retrospective study showed the median volume of resuscitative fluid was 53ml/kg. Despite the recommendation for providing large volumes of resuscitative fluid, the authors recommend providing this as 10-20ml/kg isotonic crystalloid boluses in dogs and 5-10ml/kg isotonic crystalloid boluses in cats, and then reassessing as to whether an additional fluid bolus is required.

Antihistamines are commonly used in the management of anaphylaxis; however, histamine levels rise rapidly at the onset of the reaction and decline to baseline shortly thereafter, even in the presence of significant haemodynamic instability. Combination of H1 (e.g., chlorphenamine) and H2 (e.g., cimetidine) antihistamines may be superior to monotherapy with H1 antihistamines alone in providing relief for milder clinical signs associated with type 1 hypersensitivity reactions; however, available evidence suggests they do not meaningfully alter the cardiopulmonary course of systemic anaphylaxis in dogs.

Glucocorticoids may attenuate the intermediate phase of anaphylaxis through inhibition of cytosolic phospholipase A2 while also suppressing the late phase through inhibition of cytokine production and inflammatory cell recruitment. However, the onset of glucocorticoids' beneficial effects takes several hours, regardless of the route of administration. One retrospective study demonstrated no difference in clinical improvement or survival between antihistamine monotherapy and combined antihistamine–glucocorticoid therapy in dogs with type I hypersensitivity, including anaphylaxis. The authors generally reserve the use of glucocorticoids for patients showing signs of upper airway swelling, particularly brachycephalic patients, and avoid its use in patients showing primarily gastrointestinal signs. If used, the authors tend to use a single anti-inflammatory dose of dexamethasone at 0.1mg/kg intravenously. Alternatively, and particularly in patients with vasopressor-dependent shock, a continuous infusion of hydrocortisone at 0.25mg/kg/hour could be considered.

Bronchodilators (e.g., salbutamol/albuterol) are usually given via the inhaled route to provide targeted. relief of bronchospasm, through direct action on bronchial smooth

muscle. Intravenous terbutaline could also be considered. Supplemental oxygen therapy via face mask, nasal cannulas, oxygen cage, or endotracheal tube is recommended to all patients experiencing respiratory signs, hypoxaemia, or those who are hemodynamically unstable.

Prognosis

The prognosis for severe anaphylaxis in dogs is generally favourable with appropriate treatment, with a high survival rate despite the initial clinical severity. Mortality increases in patients showing evidence of more advanced systemic dysfunction, particularly metabolic abnormalities such as hypoglycaemia or hyperphosphataemia, as well as coagulation disorders and haemodynamic compromise. Overall, these findings suggest that clinical outcome largely depends on the extent of the initial physiological derangement, with biochemical and coagulation parameters serving as useful prognostic indicators.

Case reports

Case one

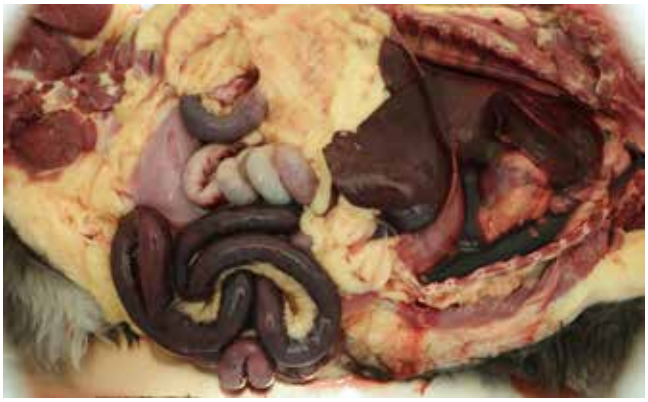
A nine-year-old female neutered Schnauzer was presented in shock after being stung by a wasp in her garden. The owners witnessed the event: initially, the dog developed irritation of the muzzle, followed by vomiting and diarrhoea that rapidly became haemorrhagic within minutes, culminating in collapse.

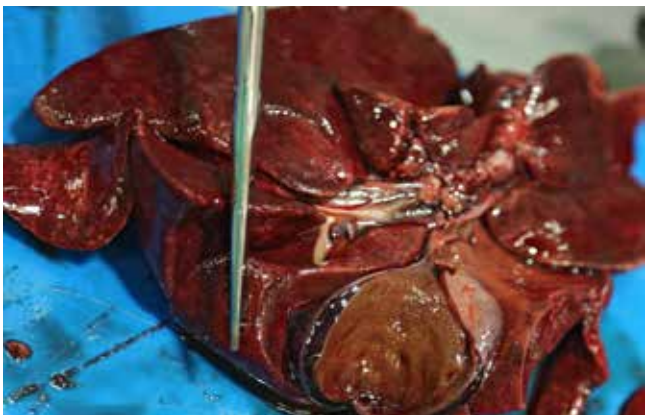
On presentation, the patient was comatose with altered mentation and showed moderate dehydration. Cardiovascular examination initially revealed a sinus tachycardia of 160bpm, with weak but synchronous pulses, mucous membranes were pale pink and capillary refill time was prolonged.

Respiratory parameters were within normal limits, with no abnormal lung sounds or cough elicited. The abdomen was distended with multiple palpable loops of fluid-filled intestines. The patient was hypothermic, with a rectal temperature of 36.8°C. Rectal examination revealed a moderate amount of haemorrhagic discharge.

A complete blood count revealed mild regenerative anaemia and marked thrombocytopenia. Serum biochemistry revealed a marked increase in ALT activity, moderate hypocholesterolaemia, azotaemia, and mild hyperbilirubinaemia. Coagulation times were prolonged.

On point-of-care ultrasound, the gallbladder wall was thickened, there was a moderate volume of free abdominal fluid. Marked distention of the stomach and the intestines with fluid material was also noted. The dog was displaying evidence of anaphylactic shock and was showing signs of disseminated intravascular coagulation (DIC) and systemic inflammatory response syndrome (SIRS). Aggressive fluid therapy was provided, and a fresh frozen plasma transfusion was administered to replenish depleted clotting factors. Noradrenaline was administered as a vasopressor; however, in retrospect, adrenaline may have been a more appropriate choice. Due to the development of hypoglycaemia, a glucose infusion was administered. Active warming was continued. Despite aggressive treatment, the dog continued to deteriorate, and given the grave prognosis, her owners elected for humane euthanasia. Post-mortem evaluation was performed, showing evidence of DIC and multiorgan failure (hepatic necrosis, acute renal tubular necrosis, adrenal necrosis, and pulmonary haemorrhage) (Figures 3 and 4) consistent with an initial shock incident (anaphylaxis in this case).





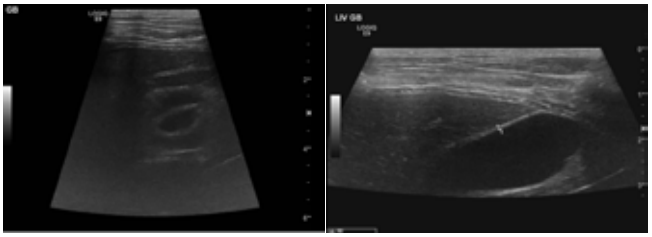
Figures 3 and 4. The top image image shows an overall view from the thoracic and abdominal cavity. The widespread haemorrhage throughout multiple organ systems (lungs, intestines, adrenal glands, liver portal areas, and kidneys) reflects the consumptive coagulopathy of DIC. The lower image shows the gallbladder and the liver with a characteristic lobular pattern, typical of shock-induced hepatic injury, where prolonged hypoperfusion causes ischaemic necrosis.

Case two

A 2-year-old male Jack Rusell Terrier was presented after being found poorly responsive and weak. There was no known antecedent event.

On presentation, the dog was collapsed. Cardiothoracic auscultation revealed a heart rate of 120bpm with no audible murmurs or arrhythmias. The femoral pulses were weak bilaterally and the mucous membranes were pale. The respiratory rate was 84 breaths per minute with normal effort and no adventitious bronchovesicular sounds. Abdominal palpation was unremarkable. There was no peripheral lymphadenopathy. The rectal temperature was 36.5°C. Systolic blood pressure was 80mmHg.

A complete blood count revealed a mildly increased haematocrit and reticulocyte count. Serum biochemistry revealed a marked increase in ALT activity and a mild hyperbilirubinaemia. Clotting times were within normal limits. Three-view thoracic radiographs were performed, which did not reveal any abnormalities. Abdominal ultrasound revealed marked gallbladder wall thickening (7mm, ref. range <1.3) with a poorly filled gallbladder (Figure 5), enlargement of the pancreas and signs consistent with pancreatic oedema. There were several loops of small intestine with mild thickening of the muscularis layer and they were moderately



Figures 5 and 6. Gallbladder progression. The image on the left shows the gallbladder wall thickening at admission. The image on the right shows the gallbladder three days later with normal wall thickness.

filled with echogenic fluid. There was a mild peritoneal effusion. Despite the initial concerning clinicopathological and imaging findings, the dog showed steady clinical improvement with fluid therapy alone. Given his positive response, his vital parameters, gallbladder wall thickness, and abdominal effusion were closely monitored. Three days later, repeated hepatobiliary ultrasound did not reveal any abnormalities (Figure 6). ALT activity remained above the reference range but had decreased. Given the acute onset of hypotension, with increased ALT activity and gallbladder wall oedema, along with rapid improvement, anaphylaxis was considered likely in this case.

Conclusion

Anaphylaxis is a severe, rapidly progressive, and potentially fatal condition that requires immediate recognition and intervention. The clinical presentation is highly variable and species-dependent, with dogs showing gastrointestinal and hepatic involvement, while cats predominantly exhibit respiratory signs.

Early onset of clinical signs is associated with greater severity, making rapid identification critical for prognosis. Diagnosis is mainly clinical and based on pattern recognition and history of exposure, as there are no specific, definitive diagnostic tests.

Anaphylactic shock is a form of distributive shock characterized by vasodilation, fluid redistribution, and cardiovascular collapse, often requiring urgent stabilisation. Prompt and aggressive treatment should be initiated before a complete diagnostic work-up, as delays can significantly increase mortality. These case reports clearly illustrate how anaphylaxis can present with highly variable severity and outcomes, reinforcing the concept described in the text that clinical manifestations are rapid, systemic, and species-dependent, with dogs frequently showing gastrointestinal and hepatic involvement.

Both cases highlight the importance of clinical pattern recognition and supportive diagnostic findings, such as gallbladder wall thickening and elevated liver enzyme activities, which are consistent with the pathophysiology of hepatic congestion described in the review. Furthermore, they demonstrate that early recognition and prompt treatment are critical but not always sufficient, as outcomes can range from complete recovery (case two) to fatal multiorgan failure (case one), emphasising the unpredictable progression and severity of anaphylactic shock.

We gratefully acknowledge the support and technical assistance provided by the pathology staff at the UCDVH Diagnostic Laboratory.

References available on request.

READER QUESTIONS AND ANSWERS

1. WHAT IS THE MAIN MECHANISM OF CLASSIC IMMUNOLOGIC ANAPHYLAXIS?

A. Complement system activation
B. IgE-mediated release of mediators from mast cells and basophils
C. Coagulation system activation
D. Direct autoimmune response

2. WHICH ORGAN SYSTEM IS MOST COMMONLY AFFECTED IN ANAPHYLAXIS IN CATS?

A. Gastrointestinal tract
B. Cardiovascular system
C. Respiratory tract
D. Nervous system

3. WHICH OF THE FOLLOWING IS A TYPICAL SIGN IN DOGS WITH SEVERE ANAPHYLAXIS?

A. Bradycardia without other signs
B. Acute haemorrhagic gastroenteritis
C. Flaccid paralysis
D. Severe hypertension

4. WHAT IS THE PRIMARY BASIS FOR DIAGNOSING ANAPHYLAXIS?

A. Specific serological tests
B. Exclusive ultrasound findings
C. Pattern recognition and clinical history
D. Tissue biopsy

5. WHICH OF THE FOLLOWING BEST EXPLAINS THE BENEFICIAL EFFECTS OF ADRENALINE/EPINEPHRINE IN ANAPHYLAXIS?

A. It reduces late-phase eosinophilic inflammation
B. It increases histamine degradation
C. It causes vasoconstriction and improves blood pressure and airway oedema
D. It directly blocks IgE receptors

ANSWERS: 1B; 2C; 3B; 4C; 5C.