



ORIGINAL ARTICLE

Clinical characteristics of two-hundred thirty-two dogs (2006–2018) treated for suspected anaphylaxis in Perth, Western Australia

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Objective To describe the clinical features of dogs treated for suspected anaphylaxis in Perth, Western Australia.

Design Single-centre observational case series with retrospective and prospective phases.

Methods This was a two-phase study of dogs with clinical suspicion of anaphylaxis presenting to the emergency service of a university teaching hospital. Dogs required evidence of, and appropriate treatment of, a type 1 hypersensitivity reaction as well as two or more organs affected (or cardiovascular signs alone) to be included. Phase 1 includes retrospective case series of 186 dogs (March 2006–December 2018). Phase 2 includes prospective descriptive case series of 46 dogs (October 2017–July 2018) focused on clinical signs.

Results In phase 1, 88 (47%) dogs had evidence of insect exposure prior to the acute event. One hundred forty (75%) dogs had dermatological signs, 141 (76%) had gastrointestinal signs and 129 (69%) had cardiovascular signs. Ninety-two (49%) dogs had vasoconstrictive shock (5 with bradycardia), 24 (13%) had vasodilatory shock, 8 (4%) had mixed vasodilatory and vasoconstrictive shock and 5 (3%) had unclassifiable shock. On focused abdominal ultrasound, 42 of 71 (59%) dogs had gallbladder wall oedema and 3 of 71 (4%) dogs had peritoneal free fluid. In phase 2, the distributions of insect exposure, organ dysfunction and sonographic abnormalities were similar to phase 1.

Conclusion Dogs presenting with suspected anaphylaxis showed a broad range of presentations. Dermatological signs were absent in a proportion of dogs, vasoconstrictive shock was more frequent than vasodilatory and unique features of shock were identified. This study highlights the challenges of diagnosis based on presenting features alone.

Keywords allergy; anaphylactic shock; gallbladder wall oedema; hymenoptera; hypersensitivity reaction; ultrasound

Abbreviations aPTT, activated partial thromboplastin time; PT, prothrombin time

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Anaphylaxis is a severe acute systemic hypersensitivity reaction resulting in multiple organ dysfunction.¹ The clinical syndrome described in dogs includes signs of

dermatological (urticaria and pruritis), gastrointestinal (vomiting and diarrhoea), cardiovascular (hypotension) and respiratory dysfunction.¹ These clinical signs have been reported in association with allergen exposure in experimental studies^{2,3} and case reports,^{4–7} and form the diagnosis of canine anaphylaxis in practice. Recent research definitions of naturally occurring canine anaphylaxis have also used these categories of organ dysfunction, integrated with consensus definitions from human medicine.^{7–12} One of these studies defined anaphylaxis as a systemic hypersensitivity reaction involving at least two organ systems, including dermatological, respiratory, cardiovascular or gastrointestinal signs.¹⁰ Several studies have followed suit with these definitions.^{8,9} Gallbladder wall oedema, peritoneal free fluid, coagulation abnormalities and an elevation in serum alanine transaminase concentration may also be present and, though they are non-specific, are often used to support the diagnosis.^{7,9,10,13}

The classic cutaneous changes in canine anaphylaxis are readily identifiable by clinicians in the setting of an acute type 1 hypersensitivity reaction.¹⁴ However, the presence of acute gastrointestinal and cardiovascular signs, in the absence of dermatological signs, can make the diagnosis more challenging. The combination of these signs in dogs is thought to arise from increased hepatic sinusoidal pressure and portal hypertension, and a subsequent decrease in venous return.^{2,3,15} Reduction in venous return should result in clinical signs of peripheral vasoconstriction though the anecdotal veterinary literature often describes anaphylactic shock to be vasodilatory in nature.^{1,16–18} The frequency of these clinical signs in a broad population of dogs with naturally occurring anaphylaxis has not been well characterised. This void of data not only creates a diagnostic challenge for clinicians, especially in the absence of a diagnostic test, but also limits the advancement of knowledge pertaining to anaphylaxis in research.

Reported allergens that are associated with anaphylaxis in dogs include Hymenoptera venom, vaccines and drugs.^{1,4,8,10,19–23} In studies based in North America and Switzerland, anaphylaxis occurring in approximately half of the dogs reported was thought to be due to Hymenoptera envenomation.^{8,10} This order of insects includes bees, wasps and ants whose venom can contain a range of chemicals, including both direct toxic components and allergenic substances to which exposed dogs can become sensitised.^{24,25} The distribution of Hymenoptera species and the composition of the venom has regional variation.^{24,26,27} Therefore, reactions to Hymenoptera venom may manifest with clinical signs characteristic of the geographic region. Given that Hymenoptera envenomation is likely the most frequent cause of anaphylaxis in dogs in Australia, it is important that regional observational data on the clinical characteristics of naturally

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occurring anaphylaxis are reported in order to guide clinicians, as well as inform future research.

The aim of this study was to describe the clinical features, treatment and outcome of dogs treated for suspected anaphylaxis in Perth, Western Australia. The first objective was to describe these features in a historical cohort of dogs presenting to the emergency service of a university teaching hospital. Given the methodological limitations of the first objective for identifying cases and characterising physical examination findings, the second objective was to describe the clinical features of suspected anaphylactic reactions in a separate smaller prospective observational cohort.

Materials and methods

This observational single-centre study consisted of two phases: a historical cohort (March 2006–December 2018; phase 1) and a prospective cohort (October 2017–July 2018; phase 2). Data collection for both phases was conducted in parallel. Both cohorts presented to the Emergency and Critical Care section of The Animal Hospital at Murdoch University.

Phase 1

A computerised medical record search was performed for the term 'chlorpheniramine' for the years 2006 to 2018, either as a billing code or as free-form text, generating an alphabetised list by client surname. The search term was selected given the presumed high frequency of antihistamine administration for any case of suspected anaphylaxis and this drug being the only injectable antihistamine used at our hospital during the study period. Additionally, use of a fee code is the most accurate method to identify cases for the computerised medical record system being used. Cases were reviewed sequentially over a 6-month period by a single investigator (K Turner), with a goal of a minimum of 300 cases meeting the following inclusion criteria: primary presentation to the emergency and critical care section, evidence of a type 1 hypersensitivity reaction and administration of a drug for type 1 hypersensitivity, such as a glucocorticoid, antihistamine or adrenaline. Evidence of a type 1 hypersensitivity reaction was defined as the primary clinician's medical record describing evidence of allergen exposure and listing type 1 hypersensitivity as the most likely differential diagnosis. Evidence of allergen exposure was defined as owner-reported observed exposure to a recognised allergen (e.g. insect or medication), clinician identification of an insect bite or sting site, or acute-onset generalised dermatological signs consistent with a type 1 hypersensitivity reaction (chemosis, urticaria [wheals and or angioedema],⁸ pruritis). These cases were further reviewed for the presence of anaphylaxis, defined as acute-onset dysfunction of 2 or more body systems, or cardiovascular dysfunction alone.^{8,10,11,28} Dogs meeting the criteria for anaphylaxis were included in the final analysis. Dogs were excluded if they were included in phase 2 of the study, if clinical signs had been observed for greater than 12 h or if there was a concurrent acute illness identified during the same visit that could explain the presenting clinical signs.

Data collected from the medical record included details on witnessed exposure to a potential allergen, description of a bite or sting site and the duration of clinical signs. Clinical signs observed by either

the owner or clinician were noted and further characterised as dermatological, cardiovascular, respiratory, neurological or gastrointestinal. Dermatological signs were defined as being an acute onset (<12 h) of generalised signs affecting the skin including urticaria, angioedema or pruritis. Respiratory dysfunction was defined as difficulty breathing, dyspnoea, hypoxaemia, stridor, stertor, tachypnoea (excluding panting) or coughing. Neurological signs included seizures, collapse or ataxia. Gastrointestinal signs included abdominal pain, vomiting, diarrhoea or signs of nausea such as hypersalivation, exaggerated swallowing or retching.

The cardiovascular data were further organised into shock categories based on patterns of findings.^{29–32} An abnormal heart rate was defined as <70 beats per minute or >120 beats per minute. Capillary refill time was recorded as rapid (<1 s), within normal limits (1–2 s) or prolonged (>2 s). Mucous membrane colour was recorded as pale (pale pink, pale or white), normal (pink) or injected (red, bright red or hyperaemic). Pulse quality was recorded as reduced (weak, poor, hypodynamic or absent), good (good, fair, normodynamic or strong) or bounding (bounding, hyperdynamic). Shock was defined by the presence of *both* abnormal heart rate and hypotension, or *one* of abnormal heart rate or hypotension with at least one abnormality of mucous membrane colour, pulse quality or capillary refill time. Dogs were further classified on the type of shock. Vasoconstrictive shock was defined by shock with at least one of pale mucous membranes, hypodynamic pulses or increased capillary refill time. Vasodilatory shock was defined by shock with at least one of injected mucous membranes, hyperdynamic pulses or rapid capillary refill time. If dogs had a mixture of signs consistent with vasodilatory and vasoconstrictive shock, they were classified as having mixed shock. If dogs had only an abnormal heart rate and hypotension, they were classified as having unclassifiable shock.

Diagnostic tests performed, medications administered, hospitalisation time and outcome were also recorded. Findings from focused abdominal ultrasonography were recorded as gallbladder wall oedema or abdominal free fluid, according to the description in the medical record.¹⁰ Fluid therapy was categorised as a continuous infusion (<20 mL/kg/hr) or a bolus (at least 10 mL/kg of isotonic crystalloid administered in less than 30 min, a fluid volume reported as a bolus or a hypertonic fluid or colloid dose administered without a recorded time frame). The total volume of fluid boluses and type of fluid was recorded. Duration of hospitalisation was grouped into 12-h blocks, as determined by hospitalisation charges.

Phase 2

Given that some clinical signs may be omitted from medical records and not all patients may be treated with chlorpheniramine, raising the possibility of missed or biased data in phase 1, phase 2 was initiated with prospective data collection. Due to the clinical importance of the diagnostic utility of clinical signs and focused abdominal ultrasonography, phase 2 focused on cardiovascular dysfunction and the observation of gallbladder wall oedema and peritoneal free fluid on focused abdominal ultrasonography. Dogs presenting to the emergency and critical care section were prospectively screened by treating clinicians for suspicion of a type 1 hypersensitivity reaction. Clinicians were advised to include any dog that they believed had a

type 1 hypersensitivity reaction of any severity as the most likely cause of the patient's presenting clinical signs. A data collection instrument was made available to all clinicians (see Supporting information S1). To reduce the risk of biasing clinicians towards including certain case types, no other inclusion criteria were provided. These cases were then reviewed for the presence of anaphylaxis, as defined by the same criteria as for phase 1. Variables included signalment, presence and duration of owner-observed clinical signs before presentation and evidence or observation of exposure to a potential allergen. Physical examination data recorded were heart rate, mucous membrane colour, capillary refill time, pulse quality, temperature, respiratory rate, blood pressure, and the presence of dermatological, gastrointestinal or cardiovascular clinical signs. Computerised medical records were reviewed by a single investigator (K Turner) to reconcile any incomplete data. Data were further categorised as described for phase 1. Dogs were excluded if clinical signs had been present for greater than 12 h.

Clinicians were requested to record still ultrasound images of the gallbladder on presentation, which were later reviewed by a specialist radiologist (N Stander) blinded to the clinician's interpretation.¹⁰ The radiologist classified the saved images as oedema present, no oedema evident or non-diagnostic. Gallbladder wall oedema was defined as a striated gallbladder wall or gallbladder wall thickness >3 mm.¹⁰

Statistical methods. Statistical analysis was performed using commercial statistical software¹. Continuous data were assessed for normality by visual examination of histograms and Q-Q plots. Continuous data are reported as median (Q1–Q3) due to non-normal distribution. Categorical data are reported as number (percentage), where data were not available for the entire sample, the denominator is provided. For frequently presented breeds (>5% of the cohort), the proportion of dogs of that breed within all dogs in this study was compared with the proportion of that breed presenting to either the emergency and critical care or primary care sections of the authors' hospital over the same time period using chi-square test, with significance set at $P < 0.05$. Given the exploratory nature of this study, and that findings are considered to be hypothesis-generating only, further statistical comparisons between sub-groups were not made.

Results

Phase 1

The first 667 alphabetised cases identified by the search were reviewed to reach 351 dogs with a type 1 hypersensitivity reaction. After further exclusions (Figure 1), 186 dogs with suspected anaphylaxis were included in the final analysis. A wide range of breeds were represented, with the most frequent (including their crosses) being 22 (12%) Staffordshire bull terriers, 16 (9%) Maltese terriers, 12 (6%) dachshunds, 11 (6%) each of Labrador retrievers and poodles. There was overrepresentation of dachshunds ($P < 0.001$), compared to a wider hospital sample. Case characteristics are described in Table 1. The most frequent allergen exposure was insect ($n = 88$; 47%), either witnessed by owner or evidence of bite/sting on presentation. Five

dogs (3%) were recently vaccinated, one received allergen-specific immunotherapy for hymenoptera venom and one received spinosad. One dog received two medications at the same time: maropitant and hyoscine butylbromide.

The distribution of categories of clinical signs, either on presentation or reported by the owners, are shown in Table 1. Only two dogs had cardiovascular signs as the only organ involvement, both of which had evidence of insect exposure. Of the 92 dogs with vasoconstrictive shock, 5 dogs had bradycardia, which also all had evidence of insect envenomation. Pertinent to cardiovascular signs there was some missing data. Perfusion parameters were not available for all dogs: heart rate was recorded in 181 (97%) dogs, mucous membrane colour in 183 dogs (93%), capillary refill time in 168 dogs (90%), pulse quality for 161 dogs (87%) and blood pressure in 106 (57%) dogs. Of the 17 (9%) dogs with neurological signs: 7 (4%) had ataxia, 4 (2%) had generalised seizure activity and one had 'convulsions'. Fourteen (8%) dogs had respiratory signs other than an increased respiratory rate reported. One dog with respiratory signs was submerged in a swimming pool in order to remove a swarm of bees and the severe respiratory distress was attributed to drowning. Another dog with respiratory signs had a brachycephalic conformation and had partial upper airway obstruction. Given the basis of the presumptive diagnosis of anaphylaxis, the distribution of clinical signs according to body system was also explored post hoc in only dogs that had evidence of insect exposure ($n = 88$; Table 1).

Packed cell volume and total plasma protein estimation, venous electrolyte and blood gas analysis, complete blood counts, various biochemistry analytes and coagulation times were performed in some of the dogs. Abnormalities in these parameters are provided in detail in Supporting information S2. Frequently recorded abnormalities were increased packed cell volume in 26 of 60 (43%) dogs, hyperlactataemia in 55 of 68 (81%) dogs, hyperglycaemia in 46 of 67 (68%) dogs and increased alanine transaminase concentration in 5 of 12 (42%) dogs. Six dogs with hyperlactataemia did not have cardiovascular dysfunction identified based on the available perfusion parameter data. Acid-base disorders were identified in 64 of 68 (94%) of dogs where a blood gas analysis was performed. The most frequent abnormality was metabolic acidosis in 33/68 (49%) dogs (Supporting information S3). Coagulation times (prothrombin time [PT] and/or activated partial thromboplastin time [aPTT]) were measured in five dogs; one dog had an increased PT and one dog had an increased aPTT. There were no coagulation abnormalities in the two dogs that had both PT and aPTT being performed. Only four dogs had a complete blood count performed therefore this data is not described.

A description of a focused abdominal ultrasonographic examination was present in the medical record for 71 dogs. Of those, gallbladder wall oedema or a halo was described in 42 (59%) dogs and peritoneal free fluid in 3 (4%) dogs. Out of these 71 dogs, 54 had cardiovascular dysfunction and, of these, 40 (75%) dogs had gallbladder wall oedema described. In contrast, of the remaining 17 dogs without cardiovascular dysfunction, only 2 (12%) had gallbladder wall oedema described. Thoracic radiographs were performed in the dog that had drowned. An electrocardiogram, with alternating sinus tachycardia and bradycardia, was recorded in one dog and a negative parvovirus faecal antigen test was recorded in another dog.

¹ SAS® 9.3, SAS Institute, Cary, NC.

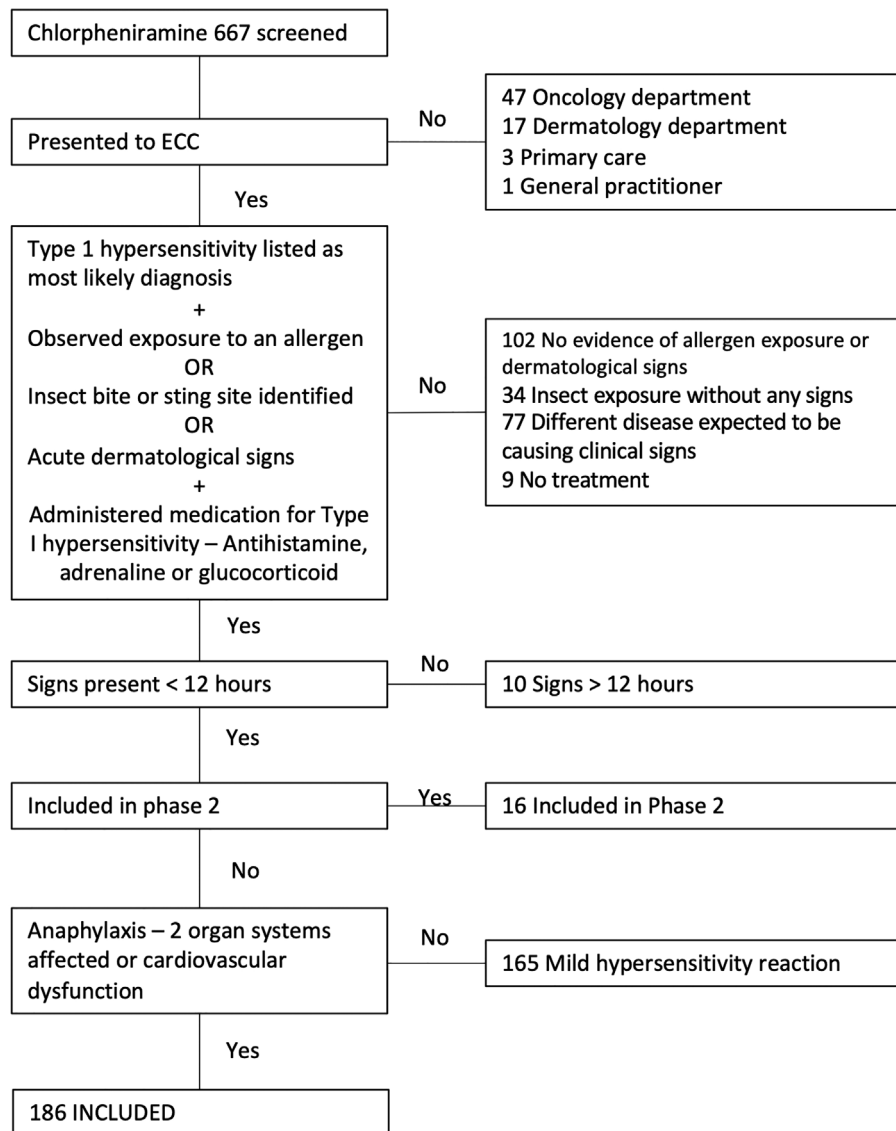


Figure 1. Study flow chart for exclusions in a retrospective cohort of dogs treated for suspected anaphylaxis.

Frequently administered medications included antihistamine, glucocorticoid and catecholamine drugs. Nineteen (5%) dogs were administered an antihistamine or glucocorticoid drug prior to arriving at the hospital by the owner or a referring veterinarian. Medications administered in hospital and at discharge have been included in table format in Supporting information S4. In-hospital medications included single injections of chlorpheniramine (175 dogs, 94%), dexamethasone sodium phosphate (43 dogs, 23%) and adrenaline (54 dogs, 29%). One additional dog received a continuous rate infusion of adrenaline. Dogs also frequently received other medications, including opioid or non-steroidal anti-inflammatory analgesics (42 dogs, 23%) and gastrointestinal drugs, such as antacids and/or antiemetics (23 dogs, 12%). Less than seven (4%) dogs each received: a sedative or anaesthetic drug, a benzodiazepine drug, atropine, oral cetirizine, fenbendazole, dopamine, noradrenaline, fludrocortisone or activated charcoal combined with sorbitol. The dog that received

activated charcoal was reported to have ingested a grape. Bolus fluid therapy was administered using an isotonic crystalloid in 65 (35%) dogs, hydroxyethyl starch 130/0.4ⁱⁱ in 12 (6%) dogs and 7% hypertonic saline in two (1%) dogs. Seventy-two (39%) dogs received isotonic crystalloid fluid as a continuous infusion including 11 dogs that were not recorded to have received a bolus. In addition to these medications, three (2%) dogs were recorded to have received oxygen supplementation. One dog presented with partial upper airway obstruction due to brachycephalic conformation and required immediate intubation. For this dog, a temporary tracheostomy and corrective upper airway surgery were performed prior to extubation.

Most dogs were discharged as outpatients shortly after arrival (108 dogs, 58%). Of the 78 dogs that were hospitalised, 69 of

ⁱⁱ Voluven® 6%, Fresenius Kabi, Friedburg, Germany.

Table 1. Characteristics of dogs treated for suspected anaphylaxis

Characteristic	Retrospective cohort		Prospective cohort	
	All dogs (n = 186)	Insect exposure only (n = 88)	All dogs (n = 46)	Insect exposure only (n = 24)
Age (years)	1.2 (0.4–5.0)	1.2 (0.4–5.0)	0.9 (0.33–2.9)	0.9 (0.4–2.7)
Sex				
Male, neutered (n)	40 (22%)	21 (24%)	13 (28%)	6 (25%)
Male, entire (n)	36 (19%)	12 (14%)	8 (17%)	3 (13%)
Female, spayed (n)	47 (25%)	32 (36%)	19 (41%)	4 (17%)
Female, entire (n)	63 (34%)	23 (26%)	6 (13%)	11 (46%)
Exposure to allergen				
Insect	88 (47%)	88 (100%)	24 (52%)	24 (100%)
Medications	8 (4%)	–	1 (2%)	–
Unknown	90 (48%)	–	21 (46%)	–
Duration of clinical signs (hours)	1.5 (0.5–3)	0.8 (0.25–2.0)	1 (0.5–1)	0.8 (0.5–1)
Clinical signs (n)				
Dermatological	140 (75%)	47 (53%)	35 (76%)	18 (75%)
Gastrointestinal	141 (76%)	76 (86%)	37 (80%)	18 (75%)
Respiratory	28 (15%)	11 (13%)	9 (20%)	6 (25%)
Neurological	17 (9%)	12 (14%)	1 (2%)	0
Cardiovascular	129 (69%)	67 (76%)	30 (65%)	17 (71%)
Vasoconstrictive shock	92 (49%)	56 (67%)	23 (50%)	12 (50%)
Vasodilated shock	24 (13%)	7 (8%)	5 (11%)	4 (17%)
Mixed shock	8 (4%)	2 (2%)	1 (2%)	1 (4%)
Unclassifiable shock	5 (3%)	2 (2%)	0	0
Rectal temperature				
Increased	19/170 (11%)	12 (15%)	5/44 (11%)	1 (4%)
Within normal limits	147/170 (86%)	67 (82%)	39/44 (89%)	23 (96%)
Decreased	4/170 (2%)	3 (4%)	0 (0%)	0

Insect exposure was defined as witnessed by owners or evidence of a sting/bite on presentation. Data are summarised as either number (%) or median (Q1–Q3). The denominator is provided for rectal temperature due to missing data.

78 (88%) were discharged within 12 h, 4/78 (5%) were discharged between 12 and 24 h and the remaining 5/78 (6%) were discharged by 48 h after admission. Two dogs re-presented following discharge: one dog presented 1 h later for new facial swelling and one presented 24 h later for recurrence of vomiting and angioedema. No dogs died naturally during hospitalisation; however, one dog, a 17.5-year-old Tenterfield terrier, was euthanased after mass bee envenomation due to severity of clinical signs and associated prognostic concerns.

Phase 2

There were 81 dogs with a case report form completed, with 46 dogs remaining after exclusions. One dog was excluded due to clinical signs being present for 16 h. The remaining 35 dogs that were excluded only had a single organ dysfunction and were therefore classified as having a mild type I hypersensitivity reaction, not anaphylaxis. Case characteristics are presented in Table 1. Similar to phase 1, evidence of insect exposure was the most frequently identified allergen exposure with 24 dogs (51%) identified. As for phase 1, the distribution of clinical signs according to body system was also

explored post hoc in this subset of dogs. One dog had exposure to a medication prior to presentation; however, this was allergen-specific immunotherapy for bee and wasp venom. The distribution of clinical signs according to organ system appeared similar to phase 1. Of the 23 dogs with vasoconstrictive shock, one dog had bradycardia and two dogs were hypotensive with otherwise normal perfusion parameters. One dog with neurological dysfunction was classified as such due to ataxia prior to presentation. All dogs were administered chlorpheniramine, five dogs (11%) received dexamethasone and 18 dogs (39%) received bolus doses of adrenaline. Medications are reported in Supporting information S4.

Results of focused abdominal ultrasonography were recorded in 38 dogs, of which, gallbladder wall oedema or halo was identified in 17 (45%). Out of these 38 dogs, 27 had cardiovascular dysfunction and, of these, 16 (59%) dogs had gallbladder wall oedema described. In contrast, of the remaining 11 dogs without cardiovascular dysfunction, only 1 (9%) had gallbladder wall oedema described. Peritoneal free fluid was recorded in four dogs, of which haemoperitoneum was diagnosed in three dogs via peritoneal fluid analysis.

Eleven dogs had ultrasound images saved for later radiologist review. Two images were determined to be non-diagnostic. Of the 9 images remaining, there was agreement between the clinician and the radiologist for 7 images (78%). One dog that the treating clinician determined had oedema, did not have oedema identified on review. One dog in which the treating clinician had not identified oedema, had mild oedema identified on review.

Discussion

This is the first study to our knowledge that describes in detail the features of clinically diagnosed anaphylactic reactions in a contemporary cohort of Australian dogs. In particular, this study documents specific abnormalities of the cardiovascular system, including clinical phenotype of shock and novel features, such as bradycardia and hypotension without other physical examination abnormalities. Unique to this study was the high number of dogs with vasoconstrictive shock, which is in contrast to anecdotal descriptions of anaphylaxis causing systemic vasodilation.^{1,16-18} Vasoconstrictive shock was frequently identified in dogs in both phases of this study. This finding was also consistent when only dogs with evidence of insect exposure were considered. The results highlight the challenge of the diagnosis itself, given the wide variability of clinical features. These results should be considered hypothesis-generating, given only approximately half of dogs had evidence of allergen exposure and the limitation of clinical syndrome definitions.

Dermatological signs are considered the classical clinical sign of type 1 hypersensitivity reactions; however, cardiovascular, gastrointestinal and respiratory signs have also been reported.^{1,8-10} This is consistent with both phases of our study, where the most frequent clinical signs were dermatological, gastrointestinal and cardiovascular. It is important to note that approximately 25% of all dogs did not have dermatological signs; this increased to 47% when only considering dogs with evidence of insect exposure. Absence of dermatological signs at varying proportions has been reported in two other recent observational studies of canine anaphylaxis.^{9,10} A comparison of the main findings of these studies is provided in Supporting information S5. Inherent to any study of anaphylaxis where a confirmatory diagnostic test is not available, there is likely some selection bias occurring, and the true proportions of these clinical signs cannot be determined. The difference in the manifestation of clinical signs may also be due to regional differences in venom,^{24,26,27} as separation of clinical signs due to type 1 hypersensitivity versus direct effects of Hymenoptera venom cannot be determined. Furthermore, the presence of a hair coat may obscure subtle skin changes, underestimating the true proportion of dogs with dermatological signs. Bearing this in mind, the lack of consistency in dermatological signs is an interesting feature of canine anaphylaxis and should not be relied upon for clinical recognition of the syndrome.

This study identified a variety of cardiovascular abnormalities in dogs treated for anaphylaxis. In veterinary medicine, anaphylaxis is often described as causing vasodilatory or distributive shock, with a possible component of hypovolaemia due to fluid extravasation or bleeding.^{16,17,33} This may have stemmed from the observation of signs of vasodilation in people with anaphylaxis.³³ However, in our

study, vasoconstrictive shock was the most frequent pattern of cardiovascular dysfunction. Data from experimental studies in dogs describe a fall in cardiac output and rise in systemic vascular resistance soon after allergen challenge, consistent with vasoconstrictive shock.^{34,35} The exact mechanisms of shock in canine anaphylaxis are not entirely understood; however, obstructive shock at the level of the hepatic vasculature remains one of the most likely hypotheses. Experimental models using histamine infusions have demonstrated hepatic arterial vasodilation, portal hypertension and hepatic venous hypotension.^{2,15,36} These changes are likely due to obstruction at the post-hepatic sinusoid blood vessels; in small hepatic venules or at the level of the hepatic venous sphincter.^{36,37} This phenomenon explains the presence of gallbladder wall oedema in clinical cases.^{7,9,10,13} Extravasation of fluid secondary to increased vascular permeability may also contribute to hypovolaemic shock, a recognised mechanism in human anaphylaxis.^{33,38,39} This response to anaphylaxis in dogs may provide some theoretical justification for blood volume expansion via the administration of intravenous fluids, despite a paucity of evidence for the efficacy of this treatment. It is currently unknown as to the clinical relevance of vasoconstrictive versus vasodilatory shock in dogs with anaphylaxis, as evident on physical examination, and any association with response to treatment or prognosis. Small sample size for dogs with vasodilatory shock precluded sub-group analysis and further research is required.

In the first phase of this study, some dogs were identified with unusual presentations of shock. However, as there was missing perfusion parameter data, we chose to investigate further with prospective data collection in phase 2. The results of phase 2 mirrored phase 1; not all dogs with shock could be classified into vasoconstrictive or vasodilatory shock, as some dogs had either a mixture of both or neither of those features. The maladaptive presence of bradycardia in the face of vasoconstrictive shock was also a unique finding in some dogs. Bradycardia paired with hypotension has been demonstrated in an experimental model of canine anaphylaxis using *Ascaris suum* injection.⁴⁰ In this study, concurrent reduction in efferent sympathetic renal nerve activity was also demonstrated. It is unknown if these dogs showed signs of vasoconstriction or vasodilation, but it is possible that this model produced a particular type of shock that lacked sympathetic nervous system response. Other experimental canine studies have not documented bradycardia.^{3,7,13,34,35,41} Relative bradycardia appears frequently in human anaphylaxis but signs of vasodilation accompany it, therefore the pathophysiology may be different to the dog.^{33,42,43} Given the presence of vasoconstriction in dogs with bradycardia in this study, a direct effect of chemical mediators on the canine myocardium may better explain this phenomenon.

The presence of gallbladder wall oedema and elevation in alanine transaminase concentration in dogs have been suggested as diagnostic tools for anaphylaxis.¹⁰ Evidence of gallbladder wall oedema in dogs in phase 1 of this study (59%) was less frequent than the observation of gallbladder wall abnormalities in the original study (93%).¹⁰ This led us to examine ultrasound images more closely in phase 2, with review by a board-certified radiologist. Based on the high level of agreement between the emergency clinician and the radiologist in phase 2, gross underestimation of the prevalence in phase 1 is considered unlikely. The decrease in frequency of

gallbladder wall oedema may be due to a number of reasons including regional variation in insect venom,^{24,26,27} differences in cause of anaphylaxis or differences in the severity of illness in the population.

Haemoperitoneum was identified in three dogs in this study. Four additional dogs had peritoneal free fluid identified, but abdominocentesis was not performed to further characterise the effusion. Although very few dogs in this study had coagulation parameters assessed, both PT and APTT elevations were identified in some of those that did. Haemoperitoneum and coagulopathy have been reported in dogs with anaphylaxis; however, the mechanism has not been determined.^{7,9,13,20} A recent abstract reported decreased antithrombin and protein C concentrations in a preliminary study in dogs with anaphylaxis, compared to healthy dogs, suggesting a consumptive process.ⁱⁱⁱ Coagulation abnormalities in people have also been reported secondary to Hymenoptera envenomation.^{44–46} The proposed mechanisms include release of heparin from mast cells, hyperfibrinolysis from tryptase production,⁴⁴ disseminated intravascular coagulopathy due to platelet activating factor release⁴⁷ and direct toxic effects of the Hymenoptera venom through the activity of phospholipase A₂.⁴⁸ The overall incidence of haemoperitoneum and coagulopathy, and the relationship between these conditions, may be underreported in this study as many dogs did not have ultrasound and coagulation testing. Anaphylaxis should be considered as a differential diagnosis for spontaneous haemoperitoneum in dogs, and further studies are required to characterise this condition.

This study has several limitations; the largest of which being missing information in medical records and lack of absolute diagnosis confirmation. We attempted to remedy this by prospective data collection in phase 2, but even with the utilisation of a data collection instrument clinicians did not always record all clinical signs or other relevant information. The identification of anaphylaxis cases was based on clinical definitions, however without a confirmatory test, it cannot be definitively proven that these dogs were truly suffering from such reaction. Although approximately half of these cases had evidence of insect exposure or envenomation, the selection of the cohort resided on clinical opinion. The use of the search term, chlorpheniramine, as the method to identify cases in phase 1 may have led to selection bias, however phase 2 also demonstrated a high frequency of the use of this drug for suspected anaphylaxis. However, case selection bias may have also occurred in phase 2 of the study, where dogs with more classic presentations such as dermatological signs may have been more frequently and rapidly recognised, and enrolled. It is also difficult to identify the true incidence of certain clinical signs, due to the bias of clinicians using an assumed pattern of clinical signs to diagnose an acute allergic reaction. This study highlights the difficulty in confidently diagnosing some cases of anaphylaxis. It is imperative that further studies investigating diagnostic tests for anaphylaxis are conducted, given the risk of misdiagnosis of cases without dermatological signs.

In conclusion, dogs with anaphylaxis in Perth, Western Australia, had a range of different presentations including dermatological, gastrointestinal, cardiovascular, respiratory and neurological signs. It is

important for veterinarians to understand the breadth of possible clinical signs of anaphylaxis to allow rapid recognition of these cases and prevent unnecessary treatment or euthanasia, especially given our finding of an excellent prognosis. Data from this study may assist clinicians in recognising cardiovascular compromise in dogs with anaphylaxis presenting with bradycardia, vasoconstrictive or mixed vasodilatory–vasoconstrictive shock. This study also demonstrated the frequency of number of presentations; phase 2 alone enrolled five cases per month, which in of itself likely underrepresents the number of actual cases seen at the hospital. Despite this likely being a very common condition treated across Australia more broadly, very little is known about the pathophysiology and treatment of the clinical syndrome. The data from this study provides further evidence to steer future research on diagnostic tests and treatment effectiveness.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site: <http://onlinelibrary.wiley.com/doi/10.1111/avj.13114/supinfo>.

File S1. Data collection instrument provided to clinicians.

File S2. Abnormalities in blood tests conducted in dogs treated for suspected anaphylaxis. Data are presented as number (% of dogs in which the test was performed). Data were classified as decreased, normal or increased according to the reference interval appropriate for the respective blood analyser.

File S3. Abnormalities in acid base analysis conducted in 68 dogs treated for suspected anaphylaxis. Data are presented as number (% of dogs in which the test was performed). Metabolic acidosis was defined as a decreased blood pH with decreased base excess. Respiratory acidosis was defined as a decreased blood pH with an increased venous partial pressure of carbon dioxide (PvCO₂). Metabolic alkalosis was defined as an increased blood pH with increased base excess. Respiratory alkalosis was defined as an increased blood pH with a decreased PvCO₂. Mixed disorders were defined as either a normal pH with changes to both base excess and PvCO₂ or if both PvCO₂ and base excess were altered consistent with acidosis or alkalosis. Data were classified as decreased, normal or increased according to the in-house reference interval established for the blood gas analyser.

File S4. Treatments administered to dogs either in hospital or at discharge for suspected anaphylaxis. Data are summarised as number (%).

File S5. Comparison of the characteristics of dogs with suspected anaphylaxis from three different regions, and the current study.

(Accepted for publication 4 August 2021)

Date:

Patient label

Acute Presentation Type 1 Hypersensitivity Reactions and Anaphylaxis in Dogs

Data Collection Sheet

For cases that you suspect have had an acute allergic reaction, such as acute onset of hives/urticaria, pruritis, facial oedema, or collapse/acute V&D (with relevant history).

History:

Owner observed exposure to a potential allergen? YES NO

Name allergen: _____

Did you find exposure to an allergen (e.g. sting)? Describe: _____

For how many hours has the dog had clinical signs before presentation? _____

Name abnormalities observed by owner (at home, **before presentation**):

GIT: _____

Skin: _____

CV (e.g collapse, ataxia): _____

Other: _____

Physical exam (at arrival): **Note time:** _____ **AM/PM**

HR: _____ RR: _____ MM colour: _____ CRT: _____ Tacky? _____ Temp: _____

Pulse quality (circle): Bounding Good Fair Weak

SBP: _____ DBP: _____ MAP: _____

Skin (circle): Facial oedema Chemosis Papules Wheals Pruritis

GIT (circle): Abdominal pain Hypersalivation Exaggerated swallowing

Vomiting Diarrhoea

Other abnormalities: _____

Other diagnostics:

AFAST: _____

Is the image of GB saved (see laminated instructions in slot)? YES NO

Bloodwork (please make sure results in record): YES NO

Other tests (please note if done): _____

Date:

Patient label

Treatments given immediately:

Drug _____ Dose _____ Time _____

Drug _____ Dose _____ Time _____

IV Fluid type _____ Volume _____ mL Speed _____ mL/hr

Physical exam (30 mins later): Note time: _____ AM/PM

HR: _____ RR: _____ MM colour: _____ CRT: _____ Tacky? _____ Temp: _____

Pulse quality (circle): Bounding Good Fair Weak

SBP: _____ DBP: _____ MAP: _____

Skin (circle): Facial oedema Chemosis Papules Wheals Pruritis

GIT (circle): Abdominal pain Hypersalivation Exaggerated swallowing
Vomiting Diarrhoea

Other abnormalities: _____

Additional Treatments:

Drug _____ Dose _____ Time _____

Drug _____ Dose _____ Time _____

IV Fluid type _____ Volume _____ mL Speed _____ mL/hr

Physical exam (60 mins later): Note time: _____ AM/PM

HR: _____ RR: _____ MM colour: _____ CRT: _____ Tacky? _____ Temp: _____

Pulse quality (circle): Bounding Good Fair Weak

SBP: _____ DBP: _____ MAP: _____

Skin (circle): Facial oedema Chemosis Papules Wheals Pruritis

GIT (circle): Abdominal pain Hypersalivation Exaggerated swallowing
Vomiting Diarrhoea

Other abnormalities: _____

Discharge medications:

Drug _____ Dose _____

Drug _____ Dose _____

Drug _____ Dose _____

Staff member who filled this out: _____

Clinician in charge of case: _____

Supporting information 2

Table: Abnormalities in blood tests conducted in dogs treated for suspected anaphylaxis. Data are presented as number (% of dogs in which the test was performed). Data were classified as decreased, normal or increased according to the reference interval appropriate for the respective blood analyser.

Parameter	Decreased	Normal	Increased
Packed cell volume	3 (5%)	31 (52%)	26 (43%)
Total protein	11 (18%)	43 (72%)	6 (10%)
Potassium	25 (37%)	43 (63%)	0 (0%)
Chloride	0 (0%)	54 (81%)	13 (19%)
Ionised calcium	3 (4%)	62 (91%)	3 (4%)
Sodium	1 (1%)	67 (99%)	0 (0%)
Glucose	1 (1%)	21 (31%)	46 (68%)
Lactate	0 (0%)	13 (19%)	55 (81%)
Alanine transaminase	0 (0%)	7 (58%)	5 (42%)
Alkaline phosphatase	1 (13%)	6 (75%)	1 (13%)
Aspartate aminotransaminase	0 (0%)	0 (0%)	1 (100%)
Phosphorus	9 (1%)	8 (73%)	2 (18%)
Albumin	3 (27%)	8 (73%)	0 (0%)
Globulin	4 (36%)	7 (64%)	0 (0%)

Supporting information 3

Table: Abnormalities in acid base analysis conducted in 68 dogs treated for suspected anaphylaxis. Data are presented as number (% of dogs in which the test was performed). Metabolic acidosis was defined as a decreased blood pH with decreased base excess. Respiratory acidosis was defined as a decreased blood pH with an increased venous partial pressure of carbon dioxide (PvCO₂). Metabolic alkalosis was defined as an increased blood pH with increased base excess. Respiratory alkalosis was defined as an increased blood pH with a decreased PvCO₂.). Mixed disorders were defined as either a normal pH with changes to both base excess and PvCO₂ or if both PvCO₂ and base excess were altered consistent with acidosis or alkalosis. Data were classified as decreased, normal or increased according to the in-house reference interval established for the blood gas analyser.

Acid-base abnormality	n (%)
Metabolic acidosis	33 (49%)
Metabolic alkalosis	0
Respiratory acidosis	4 (6%)
Respiratory alkalosis	6 (9%)
Mixed metabolic and respiratory acidosis	17 (25%)
Mixed metabolic acidosis and respiratory alkalosis	4 (%)

Supporting information 4

Table: Treatment administered to dogs either in hospital or at discharge for suspected anaphylaxis. Data are summarised as number (%)

Treatment	Retrospective cohort (n=186)	Prospective cohort (n=46)
In-hospital treatment		
Chlorpheniramine	175 (94%)	46 (100%)
Dexamethasone	43 (23%)	5 (11%)
Adrenaline	54 (29%)	18 (39%)
Analgesia	42 (23%)	2 (4%)
Antiemetic	21 (11%)	15 (33%)
Antacids	2 (1%)	5 (11%)
Antimicrobial	8 (4%)	0
Intravenous fluid	90 (48%)	15 (33%)
Crystalloid bolus	79 (42%)	14 (30%)
Hydroxyethyl starch	12(6%)	0
Hypertonic saline	2 (1%)	0
Crystalloid CRI	72 (39%)	2(4%)
Crystalloid CRI only - no bolus	11 (6%)	1 (2%)
Discharge medications		
Cetirizine	66 (35%)	16 (35%)
Chlorpheniramine	10 (5%)	11 (24%)
Other antihistamine	2 (1%)	0
Analgesia	7 (4%)	0
Antiemetic	3 (2%)	0
Antacid	6 (3%)	1(2%)
Antimicrobial	7 (4%)	0
Glucocorticoid	2 (1%)	1 (2%)
Epinephrine autoinjector	4 (2%)	2(4%)

Supporting information 5

Table: Comparison of the characteristics of dogs with suspected anaphylaxis from three different regions, and the current study.

	Current study (n=232)	Quantz et al (n=61)	Smith et al (n=67)	Rostaher et al (n=16)
Geographic region	Western Australia, Australia	California, USA	Louisiana, USA	Zurich, Switzerland
Inclusion criteria	• Clinical diagnosis • Evidence of allergen exposure (insect or medication exposure or dermatological signs) • Two or more organ dysfunction OR cardiovascular alone	• Clinical diagnosis • Known or suspected allergen exposure • Two or more organ dysfunction	• Clinical diagnosis • Two or more organ dysfunction • Severe cardiovascular or respiratory signs	• Dermatological signs plus one additional organ dysfunction
Exclusion criteria	• Concurrent illness to explain clinical signs • Signs > 12 hours	• Concurrent illness to explain clinical signs	• Concurrent illness to explain clinical signs • Signs > 12 hours	• Concurrent illness to explain clinical signs
Known or suspected insect exposure	112 (48%)	43 (71%)	Not reported	6 (38%)
Dermatological	175 (75%)	36 (59%)	18 (27%)	16 (100%)
Gastrointestinal	178 (77%)	56 (92%)	63 (94%)	14 (88%)
Cardiovascular	159 (69%)	Unable to summarise	67 (100%)	7 (44%)
Respiratory	37 (16%)	3 (5%)	45 (67%)	6 (38%)(tachypnoea only)
Neurological	18 (8%)	None reported	None reported	10 (63%)(change in mentation only)
Adrenaline	72 (31%)	Not reported	Not reported	0

administration				
Mortality	1 (0.4%)	Not reported	10 (14.9%)	0

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