Triggers, risk factors and clinico-pathological features of urticaria in dogs – a prospective observational study of 24 cases

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Background – Urticaria and anaphylaxis are frequently encountered in veterinary practice, but little is known about the causes and relative frequencies of these reactions.

Hypothesis/Objectives – This study was designed to improve current knowledge on the triggers, risk factors and clinico-pathological features of urticaria.

Animals – Twenty four dogs with signs of urticaria with or without anaphylaxis.

Methods – The study included dogs with cutaneous immediate-type hypersensitivity reactions. The cases were grouped by clinical severity into either an urticaria or an anaphylaxis group. All treatments and diagnostic tests (haematology, biochemical profile, allergy investigation) were recorded. A causality algorithm for urticaria and anaphylaxis (ALUA) was designed to determine the probability of the identified triggers and cofactors. Disease incidence, breed, age and gender predispositions were evaluated statistically.

Results – Sixteen of 24 urticaria cases were associated with anaphylaxis whilst 8 of 24 were confined to the skin. The annual hospital incidence was 0.12%. Females seemed to be over-represented (2.4:1) and most of the dog breeds were pure breed (22 of 24), with Rhodesian ridgeback, boxer, beagle, Jack Russell terrier, French bulldog and Vizslas over-represented. In addition to skin lesions, the most frequently and severely affected organ systems were the gastrointestinal and cardiovascular systems. The predominant blood abnormalities were elevated lipase and alanine aminotransferase values. Insects, food and drugs were the most commonly identified triggers.

Conclusions – To the best of our knowledge, this is the first study describing the trigger factors and clinico-pathological features of dogs with urticaria in veterinary medicine. Insects, food and drugs were the most frequently detected triggers.

Introduction

Urticaria is a disease characterized by the sudden development of wheals (hives), angioedema or both.1–4 A wheal is a transient elevation of the skin due to dermal oedema.5 Angioedema is characterized by a sudden, pronounced erythematous swelling of the lower dermis and subcutis with frequent involvement of the lower extremities and head, with or without associated wheals.6 Pruritus may or may not be present.7

Urticaria is, along with flushing and acute pruritus, one of the typical cutaneous signs of an anaphylactic reaction. These signs may occur alone or in combination with other signs of anaphylaxis. Anaphylaxis is a serious, generalized or systemic, allergic or hypersensitivity reaction with sudden onset (minutes to a few hours) that can be life threatening or even fatal.8–12

The target organs in humans often include the respiratory tract (70% of episodes) and less frequently the gastrointestinal (GI) organs (30–45% of episodes), heart and vasculature (10–45% of episodes) and central nervous system (CNS) (10–15% of episodes).8 It is generally agreed that anaphylaxis may occur with or without cutaneous signs, even though these latter signs are frequent and occur in 80–100% of cases.8,11,13 In dogs, the main shock organ is the liver leading to GI signs such as vomiting and diarrhoea (over 90%).14–18 Some GI changes may be due to direct histamine release from the intestine, but are mostly associated with mediator release directly from the liver, as shown in a study with dehepatized dogs.15,19

The cardiovascular signs are most often secondary to liver changes (hepatic arterial vasodilation and increase in hepatic portal vascular resistance).17,18 In two studies, other affected organs in dogs were the skin (ranging from 57 to 68%) and, less frequently, the respiratory and neurological systems.18,20 Interestingly, however, the highest mast cell density and histamine content after experimental anaphylaxis induction was recorded in the...
liver, skin and in particular the ear pinnae, which suggests that the skin should often, if not always, be affected, as is the case in humans. This conflicting interpretation may be due, at least in part, to the large number of differential diagnoses for anaphylaxis in the absence of skin signs.

In urticaria and anaphylaxis, activated target cells (mast cells and basophils) release histamine and other mediators (platelet-activating factor, cytokines) provoking vasodilatation, plasma extravasation and sensory nerve activation, as well as recruiting inflammatory cells to urticarial lesions. The activating signals are of immunological and nonimmunological nature. The immunological reactions are mainly immunoglobulin (Ig) E driven, although IgG or immune complexes may also be involved, with triggers such as allergens, infectious agents (bacteria, parasites) or autoantibodies. Nonimmunological urticaria and anaphylaxis (WHO recommendation: “the term ‘anaphylactoid’ should be avoided”) are caused by a heterogeneous group of mechanisms, such as heat, pressure, cold and vibration.

The diagnosis of urticaria usually is straightforward in dogs and humans due to its distinct clinico-historical pattern and scarcity of differential diagnoses. In humans, urticaria is currently classified as acute (<6 weeks duration) and chronic (>6 weeks duration). In contrast to veterinary medicine, the clinical criteria for diagnosing and grading anaphylaxis are well established in human medicine, but still under continuous debate. As mentioned above, this is largely due to the huge number of possible differential diagnoses, especially when skin signs are lacking. In this latter situation, anaphylaxis should be differentiated from all other causes of acute diarrhoea or vomiting, respiratory distress, collapse, heart failure or sudden death.

A search for a specific trigger is recommended in every patient with allergic acute urticaria and all chronic urticaria cases. In veterinary medicine, the following diagnostic tests in addition to a thorough history have been recommended: faecal flotation, diet trial, intradermal tests and/or IgE serology (mostly for insects), ice cube test and skin biopsy with histological examination. The most important triggers of anaphylaxis and acute urticarial episodes in humans are food, stinging insects, drugs, latex and atopy, premenstrual status, stress, concomitant medication (e.g. ACE inhibitors, beta-blockers) or diseases (e.g. mastocytosis, asthma). Reported risk factors and co-factors include age, allergen amount and type (e.g. peanut), atopy, premenstrual status, stress, concomitant medications (e.g. ACE inhibitors, beta-blockers) or diseases (e.g. mastocytosis, asthma).

In some cases, clinical cutaneous signs occurred in combination with systemic signs of immediate-type hypersensitivity reactions. Anaphylaxis refers to a severe, potentially fatal, systemic reaction that occurs suddenly after contact with an allergy-causing substance. Clinical criteria for anaphylaxis were adapted from human medicine. Anaphylaxis may be considered. The current recommendations for treatment of anaphylaxis depend on the disease severity and include epinephrine, fluid therapy, oxygen, glucocorticoids, antihistamines and bronchodilators.

The purpose of this prospective study was to identify the incidence, aetiology, clinical features, and the therapeutic and diagnostic approach of dogs presenting with urticaria (with/without other signs of anaphylaxis).

Materials and methods

Study design and setting

This prospective study included dogs submitted to the Department of the Clinic for Small Animal Internal Medicine and Anaesthesiology, Vetsuisse Faculty, Zurich, during a 1 year period (June 2014–2015).

Animal selection and definitions

Dogs with clinical cutaneous signs of immediate-type hypersensitivity reactions, such as urticaria, were included. Urticaria was defined as an acute onset of multiple wheals and/or angioedema. Wheals were defined as well-circumscribed, raised lesions caused by oedema within the dermis. An erythematous swelling of the lower dermis and subcutis was defined as angioedema. The diagnosis was confirmed after exclusion of other differential diagnoses (Table 1).

In some cases, clinical cutaneous signs occurred in combination with systemic signs of immediate-type hypersensitivity reactions. Anaphylaxis refers to a severe, potentially fatal, systemic reaction that occurs suddenly after contact with an allergy-causing substance. Clinical criteria for anaphylaxis were adapted from human medicine. A dog was diagnosed with anaphylaxis if, in addition to urticaria, there were signs of systemic involvement:

Patients management and data collection

Data were collected during two consecutive time periods. Immediate data collection included signalment, history and a thorough clinical examination. In the case of anaphylaxis and with owner consent, patients were immediately hospitalized and treated accordingly. Dogs without signs of anaphylaxis were followed on an outpatient basis. Some cases required additional clinico-pathological work-up, such as haematology, biochemical profile, blood pressure measurement, ultrasound, radiographs and/or skin biopsies. Records were taken of the final outcome and all diagnostic and therapeutic procedures. In addition, the history of suspected triggers and co-factors was obtained as soon as possible. Follow-up data included information regarding circumstances prior to or around the event: food consumption, utilization of drugs, observation of insect bites or stings, time of day at onset (morning, during the day, night), location (garden, during

Table 1. Differential diagnoses for wheals and angioedema

<table>
<thead>
<tr>
<th>Wheals</th>
<th>Angioedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial folliculitis</td>
<td>Juvenile cellulitis</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Infectious cellulitis</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>Mast cell tumour</td>
</tr>
<tr>
<td>Cutaneous lymphoma</td>
<td>Cutaneous lymphoma</td>
</tr>
<tr>
<td>Mastocytosis</td>
<td>Lymphoedema</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td></td>
</tr>
</tbody>
</table>

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walk, at home), exercise, stressful events, presence of estrous or pregnancy, association with physical factors (cold, heat, excessive sun, exposure, bathing).

If indicated and allowed by the owner, additional allergen tests were performed to attempt to confirm the trigger and immunological background (at least 2–4 weeks after the event). Depending on the suspected cause, skin testing (prick and intradermal) for hymenoptera, nuts and aeroallergens, in vitro testing to food allergens (Cyno-DIAL© Western blot-based test, Galileo Diagnostic by Gencils; Vadodouvre-lès-Nancy, France)40 and aeroallergens (HESKA; Fribourg, Switzerland), elimination diet, ice cube test17, autologous serum test8 and dermatographism42 were performed.

Outcome measurements and statistical analysis

Demographics and incidence
Breed, gender and age of the included population were compared to the data in the Swiss dogs registration system (ANIS) and to the data of our institution. In addition, incidence was computed by comparison to the overall number of consultations in our institution during the same time period.

Clinical signs and grading
An attempt to grade the severity of the reaction was also made (Table 2). The classification was based mainly on the affected organs and overall effect on the general condition of the dogs. Grades 0, 1, 2 and 3 refer to urticaria without anaphylaxis, mild, moderate and severe anaphylaxis, respectively.

Assessment of the causality
Assessment of the causality of allergic events is important not only in the management of patients who have experienced such events, but also for prevention of recurrence. In order to objectively determine the probability of the identified triggers, a causality algorithm for urticaria and anaphylaxis (ALUA) with a score range from 0 to 22 was designed. The principles of the Alden and Naranjo scales were followed and modified accordingly (Table 3).43,44 A cause was considered very likely or likely with ALUA values >10 and 5–10, respectively. A trigger was considered possible, but could not be confirmed, if the ALUA was <5.

Correlations
An attempt to establish correlations between overall disease severity and demographic data (age, gender, breed), trigger type, severity of skin changes (wheals versus angioedema versus both) and blood changes was made.

Statistical analysis
Numerical data such as age, weight and hospitalisation duration, were expressed as the mean, with minimal and maximal ranges. Possible age, gender and breed associations were calculated using a Fischer two-tailed exact test. Associations between different descriptive data sets were made by chi-square with Yate’s correction. All analyses were made using SPSS software v22.0 (IBM Corp; Armonk, NY, USA). Statistical significance was defined as $P < 0.05$.

Results

Incidence and demographics
Among all 20,000 hospital visits during the assessment period, 24 cases of urticaria were included in this study. The annual hospital incidence was 0.12% or 12 cases per 10,000 patients. Table 4 presents the demographic data. The average age was 4 years (0.7–11 years) and weight 21 kg (5–47.8 kg). Females outnumbered males by a ratio of 2.4:1 ($P = 0.06$).

Twenty two dogs were purebred and the following breeds appeared represented in comparison with the individual breed frequency within the Animal Identity Service Register (ANIS) Swiss reference population of the Animal Identity Service (ANIS): Rhodesian ridgeback (3 of 24, $P = 0.0002$), boxer (3 of 24, $P = 0.002$), beagle (2 of 24, $P = 0.02$), Jack Russell terrier (2 of 24, $P > 0.05$), French bulldogs (2 of 24, $P = 0.06$) and Vizsla (2 of 24, $P = 0.003$) appeared. There was no correlation between age, breed, gender and the disease severity.

Seasonality
Eleven cases were diagnosed in spring, whereas two, seven and four were seen in summer, autumn and winter, respectively. Spring seemed mainly correlated with insect bites, because 5 of 11 cases were likely to be due to insects.

Clinical signs and grading
Eight of 24 (33%) cases were considered as urticaria without anaphylaxis (grade 0) and 16 of 24 dogs (67%) urticaria with anaphylaxis. Four of the anaphylaxis group

| Table 2. Grading of disease severity in dogs with signs of urticaria and/or anaphylaxis (as adapted10,18,39) |
|-------------|----------------------|------------------|
| **Organ**   | **Urticaria**        | **Anaphylaxis**  |
| Skin        | Grade 0 (Anaphylaxis absent) | 1 (Mild)         |
|             | ≤ 1 sign from two different organ systems each Wheals, angioedema, flushing, pruritus |
| Gastrointestinal system | Single episode of vomiting/diarrhoea | Abdominal pain Persistent vomiting Persistent diarrhoea Tachycardia Pale mucous membranes |
| Cardiovascular system | None | None |
| Respiratory system | None | None |

Dyspnoea Tachypnoea Panting Cyanosis Bradypnea Respiratory arrest

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were considered mild, nine as moderate and three as severe (Table S1). The first clinical signs observed by the owner in the anaphylaxis group were the urticaria/angioedema in 8 of 16 (50% cases) and vomiting/diarrhoea in 9 of 16 cases. In three dogs with anaphylaxis, the GI and skin signs appeared simultaneously. In two of three dogs with severe anaphylaxis, the first sign was collapse; later on, all three developed angioedema and one of these also wheals. Gastrointestinal signs were present very frequently (14 of 16) and occurred several times. In the mild group, four of five showed just one episode of vomiting or diarrhoea. Almost all shock organs were affected in the moderate and severe groups (Table S2) and most of the signs related to the liver/gastrointestinal, cardiovascular and neurological systems. No severe respiratory signs were encountered; with tachypnoea as the only feature (6 of 16). Neurological signs included only changes in mentation (10 of 16 cases), with 9 of these 10 being dull and the remaining one stuporous. Six of the 16 dogs showed body temperature changes by demonstrating hypothermia and hyperthermia (three cases each).

As far as the skin changes were concerned, wheals were observed in 16 of 24 (67%) dogs (7 urticaria, 9 anaphylaxis) and angioedema in 17 of 24 dogs (4 urticaria, 13 anaphylaxis). Angioedema occurred concomitantly with wheals in 9 of 16 cases (3 urticaria, 6 anaphylaxis). Isolated angioedema was more often observed in anaphylaxis cases (1 urticaria, 7 anaphylaxis) and never related to food, but most often to insect bites (n = 4), drugs (n = 1) or unknown causes (n = 2). Erythema (pinnal and/or on other body regions) was observed in 13 of 24 cases (3 urticaria, 10 anaphylaxis). Pinnal erythema was seen altogether in seven cases (1 urticaria, 6 anaphylaxis), and was graded as mild in the urticaria group and as moderate or severe in the anaphylaxis group.

It was interesting to note that the majority of cases with reactions to insects were associated with angioedema (n = 5) whereas this change was present only in two cases of food allergy, both involving nuts. In addition, reactions to insects were more often associated with anaphylaxis (3 urticaria, 6 anaphylaxis).
Laboratory abnormalities
As expected, diagnostic investigations were most frequently carried out in anaphylaxis cases. These included haematology and biochemistry in 14 of 16 (87%) and three of eight (37%) urticaria and anaphylaxis cases, respectively. Abdominal and cardiac ultrasound examinations were performed in five and one dog, respectively, and were unremarkable. Haematology revealed leukopenia in six cases (three urticaria, three anaphylaxis) and leukenopoeia in one. In the urticaria group, no abnormalities were detected. In the analectasia group, elevated lipase (range 109–420 U/L, reference range 24–108 U/L) was observed in seven cases (one mild, five moderate, one severe). Alanine aminotransferase (ALT) was elevated in range 106–420 U/L, mean 521.4 U/L, reference range 24–617 U/L, mean 263.6 U/L, reference range 20–93 U/L from the moderate and severe anaphylaxis groups. Bilirubin and creatinine kinase were elevated in only two cases. Only one of the aforementioned dogs received glucocorticoids before the examination. No correlation between elevated lipase and the specific trigger could be found (four food, two insect, one drug). Interestingly, ALT was elevated only in hymenoptera-triggered cases.

Treatment and outcome
Interestingly, none of the cases died and the use of epinephrine was never considered necessary. The treatment of the great majority of cases was based on the use of H1 and H2 antagonists and/or glucocorticoids associated with intravenous fluid therapy (Table S3). All moderate and severe cases were hospitalized for 1.5 days on average, with the shortest hospitalization duration 4 h and the longest 4 days.

Causality (and follow-up)
Table 5 details the triggers, comorbidities and other possible risk or cofactors. The cause was identified in 17 cases and was considered very likely (ALUA > 10) in 12 (50%) and likely (ALUA = 5) in five cases (29%). These cases consisted of reactions to insect bites or stings (n = 9), foods (n = 5), drugs (n = 2) and cold (n = 1). The triggers were confirmed either with allergen tests or by observation following provocation, in 10 and seven cases, respectively. The cause could not be determined in seven cases (ALUA < 5) and the suspicion was directed mainly to foods.

Even though causality or association could not be proven, it was interesting to note that 11 cases presented with signs of atopic dermatitis (AD) and/or known food allergy history and that two dogs were treated with phenobarbital for epilepsy. One dog (number 8) was known to be food allergic but was also treated with multiple drugs, especially prednisolone and azathioprine for a concurrent autoimmune thrombocytopenia. Exercise immediately before the onset of the reaction was mentioned in the history of five dogs; stress and estrous were observed in one case each.

Six dogs were reported to have reacted to the same allergen in the past (4 urticaria, 2 anaphylaxis), with no correlation to disease severity. Most of the reactions occurred during daytime; only three were observed during the night and these were the animals with no trigger identified. All animals that

### Table 5. Triggers, comorbidities and risk/cofactors for 24 dogs with urticaria

<table>
<thead>
<tr>
<th>Causal group</th>
<th>Cause</th>
<th>ALUA score</th>
<th>Trigger probability</th>
<th>Previous episodes of urticaria</th>
<th>Concurrent allergic disease</th>
<th>Concurrent other disease</th>
<th>Concurrent treatment</th>
<th>Concurrent exercise, stress, estrous or gravidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Insect</td>
<td>Mosquito</td>
<td>6</td>
<td>Likely</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Food</td>
<td>Unknown</td>
<td>&lt;5</td>
<td>Possible</td>
<td>Yes</td>
<td>AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Physical</td>
<td>Cold</td>
<td>8</td>
<td>Likely</td>
<td>Yes</td>
<td>FA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Food</td>
<td>Potatoes</td>
<td>16</td>
<td>Very likely</td>
<td></td>
<td>AD, FA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Insect</td>
<td>Wasp</td>
<td>18</td>
<td>Very likely</td>
<td></td>
<td>Incontinence</td>
<td>Estriol</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Drug</td>
<td>Anaesthetic</td>
<td>12</td>
<td>Very likely</td>
<td></td>
<td>AD</td>
<td>Prednisolone</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Insect</td>
<td>Bee</td>
<td>6</td>
<td>Likely</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Food</td>
<td>Rice, beef</td>
<td>22</td>
<td>Very likely</td>
<td>Yes</td>
<td>FA</td>
<td>IMTP</td>
<td>Prednisolone Azathioprin</td>
</tr>
<tr>
<td>9</td>
<td>Food</td>
<td>Unknown</td>
<td>&lt;5</td>
<td>Possible</td>
<td></td>
<td>Epilepsy</td>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Food</td>
<td>Unknown</td>
<td>&lt;5</td>
<td>Possible</td>
<td></td>
<td>Epilepsy</td>
<td>Phenobarbital</td>
<td></td>
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<tr>
<td>11</td>
<td>Food</td>
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<td>&lt;5</td>
<td>Possible</td>
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<td></td>
</tr>
<tr>
<td>12</td>
<td>Food</td>
<td>Cheese</td>
<td>12</td>
<td>Very likely</td>
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</tr>
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<td>Food</td>
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<td>Possible</td>
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<td>AD, FA</td>
<td></td>
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</tr>
<tr>
<td>14</td>
<td>Food</td>
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<td>&lt;5</td>
<td>Possible</td>
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</tr>
<tr>
<td>15</td>
<td>Insect</td>
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<tr>
<td>16</td>
<td>Food</td>
<td>Walnut</td>
<td>6</td>
<td>Likely</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>17</td>
<td>Insect</td>
<td>Unknown</td>
<td>&lt;5</td>
<td>Possible</td>
<td></td>
<td>AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Drug</td>
<td>ILIT</td>
<td>12</td>
<td>Very likely</td>
<td></td>
<td>AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Insect</td>
<td>Bee</td>
<td>18</td>
<td>Very likely</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Insect</td>
<td>Bee</td>
<td>18</td>
<td>Very likely</td>
<td></td>
<td>AD</td>
<td></td>
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</tr>
<tr>
<td>21</td>
<td>Food</td>
<td>Nuts</td>
<td>6</td>
<td>Likely</td>
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<tr>
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<td>Insect</td>
<td>Bee</td>
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<td>Very likely</td>
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<td></td>
</tr>
<tr>
<td>23</td>
<td>Insect</td>
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<tr>
<td>24</td>
<td>Insect</td>
<td>Bee</td>
<td>16</td>
<td>Very likely</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALUA, algorithm for urticaria and anaphylaxis; AD, atopic dermatitis; FA, food allergy; ILIT, intralymphatic immunotherapy; IMTP, immune-mediated thrombocytopenia. No shading – urticaria without anaphylaxis; Mild grey shading - mild anaphylaxis; Grey - moderate anaphylaxis; Strong grey shading - severe anaphylaxis.
developed the first signs while being outside the house were reacting to insects. Two animals reacted to medication while in our clinic (anaesthesia and allergen-specific immunotherapy). In animals with reactions occurring while at home, the trigger was food or not identifiable.

**Discussion**

We describe herein 24 cases of urticaria with 16 of 24 of these dogs showing signs of anaphylaxis. The cause was identified in 17 of 24 and consisted predominantly of reactions to insect bites or stings (7 of 17), foods (6 of 17) and drugs (2 of 17), as reported in the human literature. Only one dog had recurrent episodes of urticaria (chronic urticaria) likely due to cold, occurring only during winter, confirming previous case reports. The cause could not be determined in seven cases, a similar rate to human studies. The triggers were confirmed either with compatible allergen tests or by observation following provocation. In order to determine the probability of various causes (very likely, likely, possible), an algorithm (ALUA) was created, utilizing the following criteria: observation of allergen exposure by owner or veterinarian, immunological evidence and positive rechallenge (Table 3). The authors would like to emphasize that this algorithm needs further validation in a larger study population.

This report also demonstrates that dogs with a history of AD seem to be at increased risk of developing urticaria or anaphylaxis regardless of cause (11 of 24 dogs). Although the worldwide or country-specific prevalence of atopy in dogs has not been determined, in humans it can reach up to 25%. Exercise immediately before or during the onset of the reaction was mentioned in the history of five dogs and in three of them the cause could not be identified, but food was suspected. These cases may represent a variant of exercise-induced anaphylaxis (with or without food association), which is a well-recognized entity in humans that remains to be further investigated. With regard to the idiopathic cases, another possible explanation to pursue in further studies based upon the human literature is the delayed anaphylaxis to red meat, provoked by the cross-reactive allergen galactose alpha-1,3-Galactose (alpha-gal) present in ticks.

Currently, no data on the incidence of urticaria or anaphylaxis in veterinary medicine exists. The European Academy of Allergy and Clinical Immunology (EAACI) Taskforce on Anaphylaxis has published, amongst others, prevalence data in people in Europe, which is estimated to be at 0.3%, whereas global data for urticaria are unavailable. Herein we show an overall incidence of urticaria with or without anaphylaxis of 0.12% or 12 cases per 10,000 dogs in a veterinary teaching hospital in Switzerland. The high proportion of dogs with anaphylaxis in this study (16 of 24 or 67%) can be explained by the hospital’s referral nature; it could also be partly attributed to the precise clinico-pathological investigation, anaphylaxis grading and case recording.

Small-size breed dogs seem to be more often associated with anaphylactic reactions, which is consistent with our findings (Jack Russell terriers, French bulldog). The rate of adverse effects due to vaccination in dogs of <10 kg is doubled, therefore, not only the type of allergen, but also its relative amount seem to play an important role in the pathogenesis of allergic reactions. Among medium- to large-size breeds, boxers, Labrador retrievers and golden retrievers are more frequently associated with anaphylaxis. Boxer dogs, Rhodesian ridgeback dogs and Vizslas were significantly over-represented in our population, when compared with the whole Swiss dog population, suggesting the animal’s genetic background as an additional pathogenetic player in the development of urticaria and anaphylaxis. In humans, epidemiological data and clinical observations suggest that gender plays a role in the development and manifestation of IgE-dependent allergic diseases, often with a female preponderance in anaphylaxis cases. Research in a mouse model showed that estrogen is not a main trigger of anaphylaxis but, importantly, increases the severity of anaphylaxis through its action on endothelial cells. Our study population consisted of more female then male dogs, although not statistically significantly. Interestingly, one case repeatedly showed urticaria only while in estrous. An association with progesterone can only be speculated, on the basis of existing human data, such cases should be followed and further worked-up.

This study showed that the liver and GI tract are the main shock organs in dogs, and this would contribute in a major way to the severity of the clinical signs with anaphylaxis. Fourteen of 16 dogs showed either vomiting or diarrhoea and also elevated ALT values, confirming findings of other studies. Serum lipase was also elevated in 8 of 16 cases, pointing toward a pancreatic disease, in part probably causing some of the observed clinical signs. This was not reported previously in dogs with anaphylaxis. In humans, mast cells are hypothesized to play a role in acute pancreatitis, which could explain these findings.

Eight of 16 dogs dogs showed cardiovascular compromise, which is consistent with the human literature and slightly less than in two previous studies in dogs. This can be explained by the fact that previous studies focused mainly on anaphylaxis and a potential selection bias could explain this discrepancy. Neurological and respiratory signs were infrequent findings and included only changes in mentation, in agreement with other reports.

Although our study population was selected by skin lesions, it is interesting to observe that skin seemed to be the first organ affected in at least 50% of all anaphylaxis cases. This could be an underestimation, as these data were obtained through owner observation. When different skin lesions (erythema, wheals and angioedema) were correlated with disease groups, urticaria versus anaphylaxis, then erythema was observed more frequently in the latter group (3 versus 10). Pinnal erythema was involved in seven of these cases, mostly in the anaphylaxis group, confirming previous findings. The low frequency of skin involvement from previous studies could be partly explained by the lack of precise dermatological observations in addition to the different clinical criteria for our study. Although not statistically significant, there was a tendency for dogs with anaphylaxis to experience more frequent angioedema without wheals. This is very likely due to the fact that these same
dogs were stung by insects, which most commonly causes deep tissue edema. Surprisingly, although angioedema was often encountered on the head region, none of our cases encountered laryngeal or other respiratory involvement as reported elsewhere. It is clear that the severity of skin lesions did not affect the patient’s outcomes, but these typical lesions (wheals, angioedema and flushing) seem to be an excellent marker for anaphylaxis, as shown in human medicine.

Although epinephrine is the mainstay of anaphylaxis therapy, its use was not deemed necessary in dogs in this study. One explanation is that the dogs recovered due to endogenous epinephrine release helping to auto-reverse the effect of biogenic amines and due to appropriate supportive treatment. The main factor explaining the reluctance to use epinephrine is the fear of adverse effects, a continuous dilemma in human medicine. Intramuscular epinephrine shows an excellent safety profile and there are no absolute contraindications for its use. It should therefore be considered for all grades of anaphylaxis, even with those with clinical features likely to evolve due to anaphylaxis. Veterinary medical publications do not list reports of life-threatening adverse effects. Grading anaphylaxis is very important in the light of therapeutic interventions, but the authors would like to emphasize here that dogs may pass through various stages of disease such that assigning each a set grade may not be appropriate. An example is chronic urticaria, a “non-anaphylactic” allergic disease, with enormous life-threatening potential.

In humans, an observation period of 6–8 h for patients with respiratory symptoms and 12–24 h for patients with hypotension and collapse is recommended due to possible biphasic reactions, but should be assessed on a case-by-case basis. An anaphylaxis veterinary review recommended 3 days, but this was not based on clinical data from studies. In our study, dogs with anaphylaxis were hospitalized for 1.5 days on average and no biphasic reactions were observed, as reported previously. Therefore, this duration seems to be appropriate and safe.

To the best of our knowledge, this is the first study describing the hospital incidence, triggering factors and clinico-pathological features of dogs with urticaria, angioedema and anaphylaxis in veterinary medicine. Insects, food and drugs were the leading triggers, resembling what is described in human medicine. As genetic predisposition, environmental factors and novel cross-reactions seem to interact to orchestrate the presentation of these reactions, much remains to be elucidated.

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les traitements et les tests diagnostiques (hématologie, profil biochimique, bilan allergique) sont enregistrés. Un algorithme de causalité pour l’urticaria et l’anaphylaxie (ALUA) a été créé pour déterminer la probabilité des facteurs et cofacteurs identifiés. L’incidence de la maladie, la race, l’âge et le genre ont été statistiquement évalués.


**Conclusions et importance clinique** – A la connaissance des auteurs, ceci est la première étude décrivant les facteurs déclencheurs et les caractéristiques clinico-pathologiques des chiens avec urticaire en médecine vétérinaire. Les facteurs déclencheurs les plus fréquemment détectés étaient les aliments, les insectes broyeurs et piqueurs et les médicaments.

**Resumen**

**Introducción** – las reacciones de urticaria y anafilaxis son encontradas frecuentemente en la práctica veterinaria, pero se sabe poco acerca de la causa y frecuencia relativa de estas reacciones.

**Hipothesis/Objetivos** – este estudio fue diseñado para mejorar los conocimientos actuales de los iniciadores, factores de riesgo y características clínico patológicas de la urticaria.

**Animales** – 24 perros con signos de urticaria con o sin anafilaxis.

**Métodos** – el estudio incluía perros con reacciones de hipersensibilidad cutánea inmediata. Los casos se agruparon según la severidad clínica en un grupo de urticaria o anafilaxis. Todas las pruebas de tratamiento diagnóstico (hematología, perfil bioquímico, investigación alérgica) fueron recopiladas. Se diseñó un algoritmo de causalidad para urticaria y anafilaxis (ALUA) para determinar la probabilidad de iniciadores identificados y cofactores. La incidencia de la enfermedad, y predisposición de raza, y género fueron evaluadas estadísticamente.

**Resultados** – 16 de 24 casos de urticaria se asociaron con anafilaxis mientras ocho de 24 permanecieron restringidos a la piel. La incidencia anual de hospital fue de 0,12%. Las hembras parecían estar más representadas (2,4:1) y la mayor parte los perros fueron de pura raza (22 de 24) con representación incrementada de las razas de Rhodesian Ridgeback, Boxer, Beagle, Jack Russell Terrier, Bulldog Francés y Viszlas. Además de lesiones de la piel, los sistemas orgánicos más frecuentemente y severamente afectados fueron los sistemas gastrointestinal y cardiovascular. Las anomalidades de la sangre predominantes fueron una elevación de los valores de lipasa y alanin-aminotransferasa. Los iniciadores implicados más comunes fueron insectos, alimentos y fármacos.

**Conclusión e importancia clínica** – a nuestro entender es el primer estudio que describe factores iniciadores y características clínico patológicas de perros con urticaria en medicina veterinaria. Los iniciadores más frecuentemente detectados fueron alimentos, insectos picadores y chupadores y fármacos.

**Zusammenfassung**

**Hintergrund** – Urticaria und Anaphylaxis werden in der tierärztlichen Praxis häufig angetroffen, aber über die Ursachen und relative Frequenz dieser Reaktionen ist wenig bekannt.

**Hypothesen/Ziele** – Das Design dieser Studie zielte auf eine Verbesserung des Wissens über auslösende Faktoren, Risikofaktoren und klinisch-pathologische Merkmale von Urticaria ab.

**Tiere** – Vierundzwanzig Hunde mit Anzeichen von Urticaria mit oder ohne Anaphylaxis nahmen an der Studie teil.


Schlussfolgerungen – Nach unserem besten Wissen handelt es sich hierbei um die erste Studie, die Auslöser und klinisch-pathologische Merkmale bei Hunden mit Urticaria in der Veterinärmedizin beschreibt. Futter, beißende und stechende Insekten, sowie Medikamente waren die am häufigsten erkannten Auslöser.

要約
背景 – 薬疹およびアナフィラキシーは動物病院において頻繁に遭遇するが、原因とそれらの反応の相対頻度に関してはほとんど知られていない。
仮説/目的 – この研究は、薬疹のトリガー、リスク因子および臨床病理的な特徴に関する最新の知識を向上させるために設計された。
供与動物 – 薬疹にアナフィラキシーが併発した、あるいは併発しなかった24頭のイヌ。
方法 – この研究には皮膚介在型過敏性反応を示すイヌを含めた。症例を臨床的な重症度により、薬疹群あるいはアナフィラキシー群分けた。すべての処置および診断的検査(血液学、生化学分析、アレルギー検査)が記録された。薬疹およびアナフィラキシーに関する因果関係アルゴリズム(ALUA)と、特定されたトリガーや補助因子の可能性を決定するために設計した。疾患発生率、犬種、年齢および性別の好発因子を統計学的に評価した。
結果 – 24頭中16頭の薬疹の症例はアナフィラキシーと関連していた一方、24頭中8頭が皮膚に限局していた。1年間の病院での発生率は0.12%であった。雌雄比率が高く認められるよう(2.4:1)、ほとんどどの薬疹群であり(24頭中22頭)、ローデシン/ルピジック、ポケケーサー、ビーグル、ジャッラッセルデーラ、フレンチブルドッグおよびピラードで、数例で強く、最も頻繁および重度に罹患していた薬剤は胃腸および心臓血管系であった。目立った薬剤の異常はリバーゼおよびアラニンアミトランスフェラーゼ値の上昇であった。、昆虫、食物および薬物が特定された最も一般的なトリガーであった。
結論 – 筆者らが知るところによれば、これは獣医学において薬疹を生じたイヌのトリガー因子や臨床病理的な特徴を解釈した最初の研究である。食物、刺咬昆虫、薬物は特定され最も頻度の高いトリガーであった。

要約
背景 – 契医臨床時には薬疹や過敏反応、食物アレルギーなど様々な原因の薬疹や過敏反応を診断し、治療することが重要である。本研究では、薬疹の原因を明らかにすることを目的とした。
仮説/目的 – 本研究の目的は、薬疹の原因を明らかにすることである。薬疹の原因として考えられる食物、虫、薬物を対象にした。
供与動物 – 本研究に用いた動物は、薬疹を発症した犬24頭である。
方法 – 本研究は、薬疹の原因を明らかにするために行った。薬疹の原因として考えられる食物、虫、薬物を対象にした。
結果 – 本研究の結果、薬疹の原因として考えられる食物、虫、薬物の頻度が明らかになった。食物では、ピーナッツが最も頻度の高い原因であり、虫では、ハエが最も頻度の高い原因であった。
結論 – 本研究の結果、薬疹の原因として考えられる食物、虫、薬物の頻度が明らかになった。食物では、ピーナッツが最も頻度の高い原因であり、虫では、ハエが最も頻度の高い原因であった。