DRUG ALLERGY IN VETERINARY MEDICINE
AWARENESS, INCIDENCE, AND CLINICAL CHARACTERISTICS

BY
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THESIS
Submitted in partial fulfillment of the requirements
for the degree of Master of Science in VMS -Veterinary Clinical Medicine
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2015

Urbana, Illinois

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ABSTRACT

The World Health Organization defines adverse drug reactions (ADRs) as “a noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment”. These ADRs can be classified into: type A reactions (60-80%, dose-dependent, predictable, and directly related to pharmacology/chemical properties), and type B reactions (20-40%, usually not dose-dependent, non-predictable). Drug allergic/hypersensitivity reactions are antigen-specific immune-mediated type B ADRs. They can be immediate (IgE-mediated; “anaphylaxis”) or delayed (IgG- or T cell-mediated). In human medicine, drug allergies are estimated to affect 0.1-3% of the general population and up to 15-20% of hospitalized patients. Drug hypersensitivity reactions appear similar clinically in dogs and humans, but their exact incidence in dogs remains unknown. Little is known about the pathogenesis of drug allergy in humans, and even less in veterinary patients. In addition, the literature about drug hypersensitivity in animals is very limited and most veterinary curricula spend little time covering this clinical issue.

For the first time in veterinary medicine, this thesis aimed to investigate the awareness of veterinarians about drug allergy and its incidence in dogs. To address these goals, we first conducted a survey to evaluate the awareness of UIUC graduate veterinarians on the topic. We also conducted a retrospective study to determine the incidence and the clinical characteristics of drug allergic reactions in dogs seen at a US veterinary teaching hospital over an 11 year-period.

We designed a survey through SurveyMonkey that targeted UIUC alumni veterinarians (n=2164) to evaluate their opinion on drug allergy in veterinary medicine. The results of this
survey suggest a lack of awareness and/or knowledge about drug allergic reactions amongst veterinarians. Our data further suggests a lack of training in veterinary medical school and a lack of information in the literature about veterinary drug allergy. Importantly, the survey also highlights the interest of the participants to learn more on the subject.

We conducted a tiered keyword search of the two clinical medical databases of the UIUC veterinary teaching hospital for the past 11 years, and thoroughly reviewed identified cases of potential drug HS. The retrospective study is the first to estimate an incidence for drug allergic reaction in dogs (0.15%), to report cases of DRESS in dogs (19 cases), and to establish an incidence for drug allergic contact dermatitis in dogs (7.7% of all drug allergic reactions). The incidence, the clinical pattern, and the drugs involved, matched what has been described in human medicine. This study also demonstrated a link between early drug discontinuation and prognosis as previously shown in human drug allergy. Importantly, the quality and completeness of the medical record were important limiting factors.

Overall, this thesis identified a lack of awareness about drug allergy in veterinary medicine, leading to a lack of or delayed recognition of these reactions, often leading to inadequate management. This work also confirmed that drug allergic reactions are potentially as frequent in dogs as they are in humans, with similar clinical patterns that can be life threatening, and therefore represents a significant issue in dogs as well. We therefore believe that improving education of veterinarians on the subject could have a significant impact. In the meanwhile, more research will be needed to better understand the impact of the drug allergic reactions in
veterinary medicine, and eventually create guidelines to improve diagnosis and management of these reactions.
ACKNOWLEDGMENTS

I would like to thank the members of my graduate committee: Drs. Karen Campbell, Jodi Flaws, and Sidonie Lavergne for the guidance they offered me. I would also like to thank Dianna Black.

This manuscript is dedicated to my parents, friends and family that supported me along the way.
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Adverse drug reactions – General introduction

The World Health Organization defines adverse drug reactions (ADRs) as “noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment”. These ADRs can be classified under two types of events. Type A reactions (60-80%) are dose dependent, predictable, and directly related to pharmacology/chemical properties. Type B reactions (20-40%) are not dose dependent, non-predictable, and if immune-mediated are called “drug hypersensitivity” or “drug allergy. These later reactions are further separated into two categories: immediate (anaphylactic) or delayed reactions. Worldwide, anaphylaxis is often defined as "a serious, life-threatening generalize or systemic hypersensitivity reaction" and "a serious allergic reaction that is rapid in onset and might cause death." These reactions are sometimes called “immediate” because they occur within 24 h of exposure to the allergen, usually in the first couple hours.

ADR incidence and reporting in human medicine

In human medicine, the adverse drug reactions are the 4th-6th cause of death. They affect 10-20% of the hospitalized patients and 7% of general population. The annual cost of these reactions, including treatment of the primary reactions, complications, and increased length of hospitalization is estimate to $500 billion in the United States.
The reporting is based on the filling of ADR reporting forms, historically called “yellow cards”. These forms are completed by the clinician in charge of the patient. These forms can be completed electronically on the Food and Drug Administration (FDA) website (www.fda.gov/Safety/MedWatch/default.htm).

In addition, pharmaceutical companies include a hotline number on the packaging of their drugs in case of questions or comments. Clinicians, but also patients themselves, can use this phone number to report an adverse reaction following the administration of the drug in question. Pharmaceutical companies compile case on a regular basis and are obligated to share them with the necessary governmental agency.

In Europe, a platform of pharmacovigilance network, called the GA₂LEN–ENDA–DAHD, centralize reports about drug allergic reactions. This network connects the European Network for Drug Allergy (ENDA) and the Global Allergy and Asthma European Network (GA₂LEN) to create the Drug Allergy and Hypersensitivity Database (DAHD).²⁰

Veterinary ADR incidence and reporting

In veterinary medicine, the incidence of ADRs remains to be established. However, similar adverse drug reactions to those reported in humans can affect veterinary patients. This is especially accurate for Type A reactions because they are linked to properties of the drug that usually remain the same between species.

FDA Center for Veterinary Medicine (FDA_CVM) is the veterinary branch of the FDA. The FDA-CVM is in charge of ADR in veterinary patients
The reporting of veterinary ADRs to the FDA was more recently developed than in human medicine, but the online reporting is similar. Reporting is accessible to the public and veterinarians and relies on voluntary reports, with a different section devoted to mandatory reporting for manufacturers of veterinary drugs.

In Australia, the Australian Veterinary Association Adverse Drug Reaction Subcommittee (ADRSC) published three ADR report between 1992 and 1996. They used the following categories to classify these reactions: 1) “definite” ADR when the ADRSC and manufacturer agree that there is no rational explanation other than an ADR for the animal’s clinical signs; 2) “probable” ADR when there is insufficient evidence to confirm an ADR, but an ADR is more likely than other possibilities and/or cannot be excluded as a possibility; 3) “non-ADR” when the case is definitely not an ADR, when there is another more likely explanation, or when there is not enough information to allow classification; 4) “unclassified” ADR if the manufacturer and the Adverse Drug Reaction Subcommittee (ADRSc) disagreed in their assessment of the report.21-23

In the UK, the Suspected Adverse Reaction Surveillance Scheme (SARSS) at the Veterinary Medicines Directorate (VMD) has been collecting ADR reports in veterinary patients since 1989.24-42 They publish annual reports that presenting the ADR per species and highly the tendency (increase or decrease), as well as the new type of ADR observed with new medication. These reports include animal reactions to veterinary drug, environmental exposure, exposure to human medications, and also the lack of efficacy of the drugs. The reporting is based on a reporting form that can be filled out by the veterinarian, the marketing authorization holders (MAHs), the general public and other organizations, such as the Animal Health and Veterinary Laboratories Agency (AHVLA) and subsequently sent for review.
UK report series show a net increase in ADR reports over the years (Fig. 1). This probably reflects an increased awareness among practitioners about this reporting system, and also the fact that the European marketing authorization allowed to raise the reporting to an international level. In addition, a European electronic ADR reporting system was set up during that period, which has eased the reporting and therefore increased veterinarians’ participation. Finally, caseloads of veterinary practices have increased during these years, which could also explain the increase in ADR reports.

Drug allergies

Types of drug allergy

Drug hypersensitivity, or drug allergic, reactions are antigen-specific immune-mediated type B ADRs. These latter reactions can be subdivided into two broad clinical categories: immediate (anaphylactic) and delayed reactions. Delayed drug allergic reactions can be mediated by either drug-specific IgG antibodies or T lymphocytes.

Drug allergy pathophysiology

Under the Gell & Coombs classification of immune hypersensitivity (Table I), anaphylactic reactions are “type I” hypersensitivity events that are mediated by drug-specific IgE antibodies. These antibodies induce mast cell and basophil degranulation, releasing very potent inflammatory molecules locally (e.g. histamine). These ADRs are called “immediate” because they occur within 24 hour of drug exposure, often within 2 hours. Delayed drug allergic
reactions, on the other end, require multiple days of exposure to the medication before the onset of clinical signs (> 5 days, but sometimes months). Importantly, this delay can sometimes be shortened to a few hours if the patient has previously been exposed to the drug. Under the Gell & Coombs classification of immune hypersensitivity, “delayed” drug allergic reactions belong to types II, III (both IgG-mediated) or IV (mediated by cytotoxic T cells). This classification is used for years, but only a few drug allergic reactions fit under those categories. Drug allergic reactions can also be classified in pseudo-allergic reactions, primarily antibody-mediated reactions and cell-mediated reactions.

The exact pathogenesis of drug allergy is still unclear. The requirement for immune sensitization is established and explains why an ADR can only be considered as a drug allergy if the patient has been exposed to the drug previously if the onset is less than 5 days. How and why the immune system becomes sensitized against a small chemical tolerated by most individuals remains uncertain. Three main theories exist to address this gap in knowledge: the Hapten Hypothesis, the Danger Theory, and the P-I Concept. In the Hapten Hypothesis, the drug is believed to be too small to be immunogenic and therefore requires to first covalently bind to a protein. In the Danger concept, the immune response to a drug-derived antigen requires the presence of co-stimulatory signals and cytokines. The danger signal might result from chemical, physical or viral stress. Finally, in the P-I concept the drug is interacting directly with T-cell receptors and MHC molecules, without covalent binding to the receptor and without priming by antigen presenting cell.

Drug allergy clinical presentation
“Immediate” type I reactions

“Immediate” drug hypersensitivity is also referred to as drug anaphylaxis or anaphylactic drug reactions. They can be defined as “a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy causing substance”. These reactions occur within 24 hours of drug exposure, usually 1 to 2 hours. The clinical presentation includes cutaneous signs, such as urticaria and angioedema, bronchospasm, vomiting, diarrhea and/or cardiovascular shock. Anaphylactic drug reactions can be life threatening, especially when they evolve towards an anaphylactic shock.

“Delayed” reactions

Delayed drug hypersensitivity reactions occur after 4-12 days after the drug therapy was initiated. It is important to note that an earlier onset is possible if the patient has previously been exposed the drug. The clinical signs involve the skin, with clinical signs as mild as a rash but potentially very severe such as Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) which carry a 10-50% risk of death even in modern human medicine. Blood cells are also common targets of delayed drug allergy: e.g. immune-mediated haemolytic anemia (IMHA), immune-mediated thrombocytopenia (“ITP”), or life-threatening pancytopenia. The liver can also be affected, sometimes leading to life-threatening hepatitis. Interestingly, delayed drug allergic reactions can lead to the development of long-lasting autoimmune diseases that will remain even after drug discontinuation: e.g. lupus, pemphigus.

DRESS cases (“Drug Rash with Eosinophilia and Systemic Symptoms”)
The DRESS syndrome is a severe form of systemic delayed drug allergy with a wide range of clinical presentations. The clinical signs can include fever (can be marked), skin lesions (often start as a rash), lymphadenopathy, eosinophilia, and internal organ dysfunction (often the liver).\textsuperscript{64,65} We used a modified RegiSCAR scale\textsuperscript{66} to identify DRESS cases among our cohort. To be included in this category, the case had to match at least 3 of the 5 following criteria: 1) suspected immune-mediated drug reaction; 2) skin lesions, that initially started with a rash; 3) fever; 4) systemic involvement including internal organs (e.g. adenopathy, hepatitis, nephritis) or peripheral lymphadenopathy; and/or 5) blood cell count abnormalities.

Allergic Contact Dermatitis

Contact dermatitis is an inflammatory response of the skin due to the direct contact between the skin and a toxicant.\textsuperscript{67} Like other ADRs, these reactions can be classified as type A or B, but they are limited to the skin. Drug allergic contact dermatitis is an immune-mediated type B reaction to a drug administered topically on the skin.\textsuperscript{67-72} Contact dermatitis represents approximatively 10\% of all dermatology visits in human medicine and is thought to represent up to 90-95\% of occupational skin diseases. Yet, the exact incidence of contact dermatitis is unclear in human medicine, and completely unknown in veterinary medicine.\textsuperscript{67}

Drug allergy diagnosis

The diagnosis of drug allergic reactions is mainly based on clinical presentation and recent exposure to a drug. Drug challenges can also be used as diagnostic tool and they are considered as very reliable.\textsuperscript{43,59,73,74} A dechallenge consists in interrupting the administration of the suspected drug to see whether the clinical signs resolve. Afterwards, a rechallenge can be
attempted by reintroducing the drug. If the clinical signs reoccur a drug allergy is highly suspicious. However, rechallenges can trigger life threatening reactions and are therefore not commonly recommended. Yet, these rechallenges can sometimes be performed involuntarily during the course of the patient therapy and the thorough review of the therapeutic history is primordial.

Skin tests to diagnose drug allergic reactions include prick testing, patch testing, and intradermal testing.\textsuperscript{43} These tests were developed and validated to test allergic reactions to environmental allergens in human patients, such as hay fever. These tests have shown very good results with immediate reactions to $\beta$-lactam antibiotics in humans, but their reliability appears very limited for other types of drug allergic reactions.\textsuperscript{43,75-77}

Ex vivo diagnostic tests, such as the Lymphocyte Transformation Test (LTT), exist, but are not widely available. The LTT consists in exposing patients’ leukocytes to the suspected drug in vitro and measuring any subsequent drug-induced cell proliferation.\textsuperscript{78,79} Indeed, lymphocytes will only proliferate in vitro if they are exposed to the antigen they are sensitized against. The LTT has a reported sensitivity of 60-70\% and a reported specificity of 85–93\%, but these rates are significantly increased when patients are properly selected before testing to confirm the probability of the reaction (e.g. accurate timeline of events, adequate clinical signs).\textsuperscript{78}

The use of algorithms in diagnosing ADRs has been described in human medicine.\textsuperscript{80} These algorithms are more easily used for type A reactions where clinical signs have already been clearly established. However, they can be applied to drug allergic reactions as well.\textsuperscript{81} Specific algorithms have recently been established for drug allergic reactions.\textsuperscript{7,20} They analyse the history of the patient (timing, previous exposition), results of diagnostics tests (skin prick test, skin intradermal test), and provocation test.
Drug allergy management

The discontinuation of the culprit drug is the keystone component of the treatment.\textsuperscript{1,7,43,55,82-84} Supportive care is sometimes needed with certain clinical presentations: e.g. topical treatment with open skin lesions; blood transfusion with anemia; antihistamines with urticarial; or IV fluids with shock. The prognosis will depend a lot on the early recognition of the reaction, the early withdrawal of the drug and the target organ.\textsuperscript{85}

Drug allergy epidemiology

Incidence

In human medicine, the exact incidence of drug allergic reactions is not fully determined as studies have usually focused on specific patient populations (e.g. HIV+ patients).\textsuperscript{7} In addition, methodologies vary significantly between published reports; some having included reactions self-reported by patients while others only included reactions confirmed by a clinician; some studies focused on electronic records within one given hospital while others included reports from national reporting databases. However, drug hypersensitivity reactions are thought to account for 1/3 of all ADRs and are thought to affect 0.2 -3\% for the general patient population, and potentially up to 15-20\% of hospitalized patients.\textsuperscript{86-92}

In veterinary medicine, the incidence of drug allergic reactions has never been investigated. However, drug allergy experts believe it is similar to what is observed in humans when
considering veterinary patients such as dogs who often receive similar drugs for similar diseases than their human counterpart.43

Predisposing factors

The existence of predisposing factors to drug allergy has never been investigated in veterinary medicine. However, there is some evidence suggesting that women might be more commonly affected by drug allergy than men.93-95 Pre-existing immune disorders, such as asthma and systemic lupus erythematosus, appear to increase the risk of drug allergic reactions.1,96,97 Interestingly, infectious diseases, such as chronic viral infections (e.g. herpes and HIV)98 or recurring bacterial infections (e.g. cystic fibrosis)99 seem to also be associated with an increased risk of drug allergy that goes beyond increased drug exposure.100

Pharmacovigilance & reporting

During drug development, clinical trials include relatively small number of patients, decreasing the likelihood of observing drug allergic reactions that often have an incidence of 1% or less. Post-marketing pharmacovigilance therefore plays a primordial role in tracking drug allergy. Yet, to date, none of the ADR reporting systems presented above, properly separate drug allergic reactions, limiting their usefulness in the field of drug allergy.

Training, knowledge and awareness about drug allergy among clinicians

Underreporting and misdiagnosis of drug allergic reactions also affect their clinical outcome.101,102 Thus, the early recognition of a drug allergic reaction leading to early
discontinuation of the culprit drug reaction has specifically been associated with a better prognosis in human medicine.\textsuperscript{1,7,55,83,84}

In 1976, Inman discussed these issues in his so-called “seven deadly sins”: 1) “complacency”, encouraged by the one-sided drug promotion and belief that only safe drugs are allowed on the market; 2) “fear” of possible involvement in litigation or investigation of prescribing costs by the Health Departments; 3) “guilt” of having administered the treatment which may have harmed a patient; 4) “ambition” to collect and publish a personal series of cases; 5) “ignorance” of the Committee’s requirements for reporting; 6) “diffidence” about reporting mere suspicions; and finally 7) “indifference” on the part of an individual doctor to his/her essential role as a clinical investigator who should be contributing to the general advancement of medical knowledge.\textsuperscript{103} We and others believe that these sins also apply specifically to drug allergy, with an even stronger emphasis on lack of knowledge since these drug reactions represent an even smaller proportion of pharmacology teaching than general ADRs in medical and veterinary schools. For instance, the lack of knowledge about drug allergy in human medicine has been associated with an increased risk of mis- or delayed diagnosis, further leading to inappropriate management, increased costs, and decreased prognosis.\textsuperscript{104-106} Inaccuracies in the interpretation of drug allergy diagnostic tests have also been documented in surveys about drug allergy in human medicine.\textsuperscript{104,105}

Concluding remarks & Thesis goals

Little is known about drug allergy in veterinary medicine. The literature is sparse and the incidence of drug allergic reactions remains unknown. For the first time in veterinary medicine
to our knowledge, our thesis aimed to investigate the awareness of veterinarians about drug allergy and its incidence in veterinary patients. To address these goals, we first conducted a survey to evaluate the awareness of UIUC graduate veterinarians on the topic. We also conducted a retrospective study to determine the incidence of drug allergy in dogs seen at a US veterinary teaching hospital, and to further define the clinical characteristics of these reactions.
### Table I: Gell & Coombs Classification of Drug Hypersensitivity

<table>
<thead>
<tr>
<th>IMMUNE REACTION</th>
<th>MECHANISM</th>
<th>EXAMPLES OF CLINICAL MANIFESTATIONS</th>
<th>TIMING OF REACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (IgE-mediated)</td>
<td>IgE mediated mast cell degranulation</td>
<td>Urticaria, angioedema, bronchospasm, anaphylactic shock</td>
<td>&lt;24h</td>
</tr>
<tr>
<td>Type II (cytotoxic)</td>
<td>Ig M/G induced cell lysis</td>
<td>Blood dyscrasia</td>
<td>&gt; 5 continuous days of exposure (shorter at reexposure)</td>
</tr>
<tr>
<td>Type III (immune complex)</td>
<td>Drug-Ig M/G complex deposition and/or complement activation</td>
<td>Arthropathy, nephritis, cutaneous vasculitis</td>
<td>&gt; 5 continuous days of exposure (shorter at reexposure)</td>
</tr>
<tr>
<td>Type IV (delayed, cell-mediated)</td>
<td>Cytotoxic T cells</td>
<td>Allergic contact dermatitis, toxic epidermal necrolysis, hepatitis</td>
<td>&gt; 5 continuous days of exposure (shorter at reexposure)</td>
</tr>
</tbody>
</table>
Modified from ‘Clinical Aspects of Immunology’^{47}
FIGURES

Figure 1: Increase in ADR reports for dogs over the years in UK.
REFERENCE LIST


CHAPTER 2

DRUG ALLERGY SURVEY OF THE ALUMNI OF THE COLLEGE OF VETERINARY MEDICINE AT THE UNIVERSITY OF ILLINOIS.

ABSTRACT

Drug allergic reactions are immune-mediated adverse drug events: “immediate” IgE-mediated (≈1/3) or “delayed” IgG/T cell-mediated reactions. This topic is rarely taught in any detail during veterinary training, decreasing clinicians’ awareness and preparedness to diagnose and manage these reactions. We therefore designed a survey through SurveyMonkey that targeted UIUC alumni veterinarians (n=2164) to evaluate their opinion on this matter. Over 8 weeks, the survey received a 12.9% rate. 43.8% of responders believed their curriculum had not prepared them adequately to diagnose and treat these reactions; 33.6% indicated that they never received any information about drug allergy during their training; and 50.6% that there isn’t enough information in the veterinary literature. Yet, 78.3% estimated seeing 1-12 confirmed or highly suspicious cases/year, 9.6% 13-24 cases, and 1.7% 25-60 cases. Participants indicated that drug allergy usually involves: skin (97.6%), GI (89.2%), respiratory (88.8%), cardiovascular (77.3%), and blood (69.3%). Initially, most included clinical signs compatible with anaphylaxis only (83.1%), rather than delayed reactions (1.0%) or both (15.9%). However, after reading a short informative paragraph about drug allergy, 30.8% participants indicated that they would include drug allergy more often in their differential diagnosis and 45.1% that they would start asking about past drug allergy. Finally, 87.7% indicated being interested in learning more about drug allergy as part of their continuing education in the future. In conclusion, this survey suggests that
there might be a lack of awareness secondary to a lack of teaching specific to drug allergy in veterinary medicine, like has been identified in human medicine previously.
INTRODUCTION

The World Health Organization defines adverse drug reactions (ADRs) as noxious, unintended, and undesired effects of a drug that occurs at doses used for prevention, diagnosis, or treatment. “Drug hypersensitivity” or “drug allergic” reactions are antigen-specific immune-mediated type B ADRs.1-7 These latter reactions can be subdivided into two broad clinical categories: immediate (anaphylactic) and delayed reactions.5,8

Little is known about drug allergic reactions in veterinary patients. Most veterinary curricula include little training about them. In addition, little literature has been published on the subject in veterinary medicine. Drug hypersensitivity reactions in dogs appear to have a similar clinical pattern to those reactions seen in humans,8 and the little research that has been conducted on the pathogenesis of these reactions in this species revealed similar biomarkers.9-11

In human medicine, the early recognition of the reaction associated with the early discontinuation of the suspected drug is associated with a better prognosis.2,12-15 Yet, the lack of awareness and reporting is still one of the major issues in the prevention, proper diagnosis, and treatment of drug allergy, and this significantly affects the estimation of its incidence.16,17

The present survey was designed to evaluate the awareness towards drug allergy amongst veterinarians that graduated from the University of Illinois College of Veterinary Medicine.
METHODS

Survey target population

The survey targeted veterinarians who graduated between 1974 and 2014 from the College of veterinary Medicine at the University of Illinois, and who had agreed to be contacted by the alumni office for such research or public relation endeavour (n=2164).

Survey format

This online survey was built within, and sent out by, the SurveyMonkey interface. A personal link to the survey was included in the email received by the target population. Participants were able to save their answers if they could not finish the all questionnaire in once. The participants were not allowed to go backward in the questionnaire. A “skip” option was available for questions that were not relevant to the participant. Reminders were sent by email through SurveyMonkey.

Survey questions

The questionnaire was submitted to, and approved by, the University of Illinois Institutional Review Board (IRB). The first section of the questionnaire was aimed to define the characteristics of the population sample, such age, gender, professional occupation, professional location, clinical specialization, research. The second section covered the general knowledge about drug allergy, acquired during the veterinary training at UIUC or through readings and conferences after graduation. The third section was focused on drug allergy cases that the responder sees or used to see in practice: rough incidence, clinical patterns and prevention plan.
Mid-survey, a brief informative paragraph about drug allergy (appendix) was introduced before some questions were repeated. Finally, the last section inquires about the interest of the responder to have more information about drug allergy and their willingness to consult a specialist for cases. The entire questionnaire is available by email request to the authors (appendix).

Survey pre-testing
First, we asked some non-veterinarians (n=5) to evaluate the question clarity and the software interface. After a few minor modifications of the questionnaire, a beta-test was realized with a few veterinarians that were not UIUC alumni (n=12). This led to a few additional minor changes.

Survey management
The survey was first sent on October 27 2014. Reminders were sent before the survey was officially closed 8 weeks later. During the following spring, an email was sent to people with active email addresses who did not participate although they did not opt out. This follow-up email (pre-approved by the IRB office) aimed to understand what factors could have influenced their decision not to participate.

Survey data analysis
The data were collected from SurveyMonkey in an excel format. Answers to the open questions were reviewed and categorized individually. Categorical answers were summarized automatically into the SurveyMonkey report.
Statistical analysis

Some descriptive statistics were calculated whenever possible: mean, median, standard deviation, range. In addition, an interval-censored life table with a gamma-distribution model was used to compare answer series for questions that were asked before and after the informative paragraph. P values inferior to 0.05 were considered as the threshold for statistical significance.
RESULTS

Response rate

Survey Monkey reached out to 2164 email addresses provided by the alumni office. Ten people had opted out of SurveyMonkey (in general, not specifically for our survey). In addition, the message bounced from 15 email addresses. The survey therefore really reached 2139 persons, out of which 275 participated in our survey (12.9 % response rate). Incomplete questionnaires were submitted by 37.5% of the responders.

Our follow-up inquiry to alumni who did not respond is still underway. At this time, 28 of the 1808 persons contacted replied to this follow-up email. Their responses can be categorized as follow: 32.7% did not participate in our survey because they did not feel they had anything to say on the topic; 28.6% did not participate in our survey by lack of time; and 10.7% did not participate in our survey because they missed the emails. (Table X)

Responders’ characteristics

Amongst the respondents that indicated their gender (N=268), 66.4% were women and 33.6% men. Based on the 242 respondents who indicated their age (88%), their answers ranged from 26 to 68 years of age (median of 41).

Of the 254 respondents who indicated their year of graduation, 2001 was the median (range: 1974 – 2014), and 36.6 % of the responses came from veterinarians who graduated within the last 5 years. Of the 265 participants who indicated their location, 98.9% work(ed) in the United States of America, 54% of which in Illinois specifically.
Among the 252 respondents who indicated their professional activity, 80.6% are currently working as clinicians and 13.1% used to; 24.5% works or worked in academia, 7.1% in industry, and 5.6% in a governmental agency. Among the clinicians (N=258), 93.2% work/worked in private practice; 79.5% mainly treat/treated dogs and cats, 5.8% horses, 2.7% exotics and wildlife, and 1.6% food animals. Forty-two responders (15.4%) are Board Certified Specialists (n=34) or in training (n=3) (Fig 2-A). Fifty-six responders (19.3%) pursued, or are pursuing a degree in research (Fig 2-B).

Training about drug allergy

When we asked our participants whether they attended a lecture, laboratory, discussion, or school seminar about drug allergy during their DVM training at the UIUC College of Veterinary Medicine, 29.8% of the 265 answered “yes”, 33.6% “no”, and 36.6% “do not remember”. Twenty-six percent of the responders indicated that the information regarding drug allergy in their veterinary curriculum was sufficient to diagnose and treat drug allergic reactions with confidence, but 43.8% did not and 27.9% did not know.

Since graduation, 16% of 266 responders mentioned having attended a presentation about drug allergy, mainly during a conference (50%), but also continuing education (5%), seminar series (5%), residency training (2%), and hospital rounds (2%). Sixty-one percent (N=265) indicated having read some articles on drug allergy since graduation. Interestingly, 50.6% of the participants (N=265) indicated that the information on drug allergy in the veterinary literature is insufficient in their opinion.

Number of cases of drug allergy
To the question “How many confirmed or highly suspicious cases of drug allergy do you see per year (on average)?”, 10.4% of the participants answered “none”, 78.3% “1 to 12”, 9.6% “13 to 24”, 1.7% “25 to 60”, and none chose the “>60” option (Fig 3). Interestingly 78 out of the 235 responders (33.2%) indicated that they would change their answers after reading the informative paragraph about drug allergy. Amongst the 76 responders that changed their answers, all increased the number of suspected or confirmed cases of drug allergy seen per year (Figure 3), leaving us with no “none”, 51% of “1 to 12”, 33% of “13 to 24”, 13% of “25 to 60”, and 3% of “>60”. The difference in answer profile to this question before and after the informative paragraph was statistically significant (P<0.001).

Clinical approach

To the question “When you take the history of a patient, do you or your technician ask specifically whether this patient has any known drug allergy?”, 22.3% of the participants (N=238) answered ”never”, 43.7% ”sometimes”, 19.3% “most of the time”, and 14.7% ”always” (Fig 4). Interestingly, after reading the informative paragraph, 45.1% of the responders (N=233) indicated that they would start asking for previous drug allergy if they did not until now.

When we asked how often the responders usually include drug allergy in their differential diagnosis, out of N=241 5.8% chose “never”, 89.6% “sometimes (1-25% of your patients)”, 3.3% “regularly (26-50% of your patients)”, 1.2% “often (51-75% of your patients)”, and none answered “almost always (76-100% of your patients)” or “always (all of their patients)” (Fig 5). After reading the informative paragraph, 30.8% of 237 indicated that they would change how
often they include drug allergic reactions in their differential diagnosis, 36.7% that they might, and 32.5% that they would not.

When asking if the responders warn/warned owners specifically about the risk of allergic reaction to the drugs they prescribed their pet, 13.4% answered “never”, 48.7% “sometimes”, 28.2% “most of the time”, and 9.7% “always” (N=238). After reading the informative paragraph, 157 participants modified their responses and the percentages changed to 1.3%, 48.5%, 30.6%, and 19.7% “always” (Fig 6).

We also asked these clinicians whether their medical records include/included a warning system if a patient had a history of suspected or confirmed drug allergic reaction (e.g. sticker, tag, alert message in the electronic system). Out of the 239 responses, 79.9% were “yes”, 15.1% “no”, and 5% “did not know”.  

Clinical presentation

We asked the responders to list the clinical signs that they would associated with a drug allergic reaction. When analysing these answers for each responder individually, 83.1% of the responders (N=239) indicated only clinical signs matching anaphylaxis (e.g. angioedema, urticaria, respiratory distress); 1.0% indicated only clinical signs matching delayed reactions (e.g. Erythema Multiforme, Stephen Johnson Syndrome, ITP, IMHA); and 15.9% indicated clinical signs compatible with both types of drug allergy (e.g. dermatologic signs, skin eruptions) (figure 6A, table II-VII). When analysing all the clinical signs given by the responders 41.1% of the clinical signs were specific of immediate reactions, 8.1% were specific of delayed reactions, 9.7 were compatible with immediate and delayed reactions, and 40.5% were relates to any type of drug allergy, but to Type A ADR. (Fig 7B).
After classification per organ system of each individual answer of the participants, the skin was the most commonly cited (100%), followed by the gastrointestinal tract (70.7%), the respiratory tract (22.2), the nervous system (31%), and the cardiovascular system (13.4%) (Fig 8).

After this open-ended question, we asked participants to select some organ systems that may be targeted by a drug allergic reaction from a pre-set list. Out of the 251 persons who answered this question, 97.6% selected the skin, 89.2% the gastrointestinal system, 88.8% the respiratory system, and 77.3% the cardiovascular system (Fig 8).

When we asked about the type of blood work abnormalities that the participant might associate with a drug allergic reaction, cell blood count abnormalities was the most common 75.6%, followed by liver enzymes changes 34.9%, and kidney parameters changes 12% (Table VIII). Amongst the blood abnormalities, eosinophilia was the most commonly mentioned (34.9%), followed by anemia (26.8%), leukocytosis (19.1%), and thrombocytopenia (13.4%) (Table IX).

Responder’s wishes

Among the 252 participants who answered this question, 87.7% indicated being interested in learning more about drug allergy as part of their continuing education. When asked which method they would prefer for this purpose, they proposed the following options: national or regional conferences (63.3%); in-house or university seminars (52.3%); journal articles (62.4%); or online (49%; e.g. webinars or Veterinary Internet Network, VIN). Among the 253 participants who answered the question, 79.4% indicated that they will consider consulting with an expert on drug allergy in the future for specific cases.
DISCUSSION

This survey aimed to evaluate the awareness about drug allergy among veterinarians who graduated from the College of Veterinary Medicine at the University of Illinois. To our knowledge this is the first veterinary survey on drug allergy.

Our 12.9% response rate is in the low range (9.1-37%) of response rates among the 4 surveys published in veterinary medicine that did report their response rates (out of 10 veterinary surveys indexed in PubMed).\textsuperscript{18-21} Our response rate is also lower than the surveys obtained in the 3 published surveys on drug allergy in human medicine (31.8-48%).\textsuperscript{22,23} This relatively low rate was probably multifactorial.\textsuperscript{24,25} First, the participation to our survey was voluntary and did not have any incentive that could increase the participation rate. However, we specifically targeted UIUC alumni to decrease the need for an incentive. In addition, the survey might have been too long for clinicians to fill it out at work; 28.6% did not participate in our survey by lack of time. However, the format allowed them to save their answers and complete the surveys not all at once. It is also possible that the email list provided by the alumni office was not fully up-to-date. Indeed, these email addresses are updated only on voluntary basis.\textsuperscript{24,25} Interestingly, over 10% of people who replied to our follow-up email indicated that they missed the emails asking them to participate to our survey. Finally, it is possible that the low rate itself shows the lack of awareness and/or interest of the veterinarians contacted about drug allergy. Thus, 32.7% of people who replied to our follow-up message indicated that they did not participate in our survey because they did not feel they had anything to say on the topic.

The male: female gender ratio among US veterinarians is 0.8 [AVMA website] compared to 0.5 in our sample. This difference can be explained by a different gender ratio amongst the
UIUC alumni, but for confidentiality reasons, researchers do not have access to the gender information of registered alumni. It is important to note that the gender ratio on the AVMA website is only based on employed veterinarian while our survey also included retired veterinarians.

The proportion of board-certified specialists among the US veterinarians is 11.5% [AVMA website] against 15.4% in our sample, which is not statistically different. This could be relevant because residency programs preparing veterinarians for board examinations likely increase the opportunities for these clinicians to learn about drug allergy.

Our sample includes a significantly higher percentage of clinicians working in private practice (93.2%) compared to US veterinarians (60.0%, 2014; P<0.0001). [AVMA website] Amongst the responders working as clinicians, most worked with dogs and cats (79.4%), which is similar to the general US veterinary population (75.1%). [AVMA website] This could be relevant because most of the studies about veterinary drug allergy were about dogs and cat. Small animal practitioners might therefore be more likely to have read on the subject.

Only 26% of our responders felt that the information provided during their training about drug allergy was sufficient to recognize and treat these cases. Only 1/3 of the participants remember having attended a lecture, laboratory, discussion, or school seminar, about drug allergy during their DVM training at the UIUC College of Veterinary Medicine. This observation can most likely be extended, indeed the AVMA regulates the curriculum in all US veterinary schools, and they do not require of the coverage of drug allergy into any detail (https://www.avma.org/ProfessionalDevelopment/Education/Accreditation/Colleges/Pages/coe-pp-requirements-of-accredited-college.aspx). Interestingly, a third of our responders (31.5%) graduated within the last 5 years, which coincides with the arrival of a drug allergy specialist at
UIUC. These responders may have been more sensitive to the topic because they were more exposed to it during their training, through lectures, electives, or research seminars. In human medicine studies have shown that the lack education on drug allergy delays their diagnosis and treatments.\textsuperscript{22,28} It is important to note that, in the US, the AVMA regulates the material taught in all certified veterinary schools. To date, they do not require for drug allergy to be covered.

Only 16\% of our survey responders have apparently attended a presentation on drug allergy since graduation. This can be explained by the very limited number of experts in veterinary drug allergy. The topic is discussed annually at non-veterinary conferences like the Society of Toxicology (SOT) meeting. It even has its own international meeting: Drug Hypersensitivity Meeting (DHM) since 2004. However, drug allergies are rarely discussed at conferences more commonly attended by veterinarians, even less so at meetings targeting general practitioners. The responders would be interested to learn more about drug allergy during national or regional conferences (63.3\%); in-house or university seminars (52.3\%).

In human medicine, a survey specifically looked at the impact of an educational program focused on drug allergy (penicillin) on their clinical management in the US.\textsuperscript{22} Clinicians were surveyed 6 week after an educational initiative and the implementation of clinical guideline for the cases of drug allergy. They found that the clinicians had a better understanding of how to use and interpret the diagnostic tests after the presentation, therefore the diagnostics were more accurate as well as the management of the drug allergy cases. They conclude that the increase of knowledge and the guidelines were beneficial for the practice.

Half of the responders (50.6\%) thought that the information about drug allergy in the veterinary literature is insufficient. Indeed, when searching PubMed, only 19 (12 case reports, 2

40
primary research articles, and 4 reviews) can be.\textsuperscript{8,26,27,29-42} The majority of the participants (62.4\%) indicated being interested in learning more about drug allergy by in journal articles.

Interestingly, after our short informative paragraph about drug allergy, the estimated number of drug allergy cases seen per year significantly increased (Fig.2). This illustrates that personal knowledge about drug allergy can affect how a veterinarian estimate its importance in his/her own practice, linking lack of knowledge and underestimation. This also suggests that a significant number of these veterinarians might have misdiagnosed some cases of drug allergy in the past.

After reading this informative paragraph, multiple participants also indicated that they would start asking for previous drug allergic reactions when taking the history and warning the owners about drug allergy when prescribing a drug (Fig 4 & 5). Multiple responders also indicated that they would change how often they would include drug allergy in their differential diagnosis (Fig 6). This further illustrates that improving education on drug allergy could improve their prevention and/or their recognition.

The majority of responders (\sim 70\%) described clinical signs associated with immediate reactions, such as cutaneous signs (angioedema or urticarial), respiratory distress, or gastrointestinal signs. Yet, in human medicine, immediate reactions represent only 30-40\% of drug allergic reactions.\textsuperscript{3,8,43-48} Only 16.9\% of responders mentioned clinical signs that can be associated with delayed reactions: 7.1\% mentioning skin lesions associated with delayed reaction (e.g. erythema multiforme, toxic epidermal necrolysis), 5.9\% blood cell abnormalities, and 2.9\% liver problems (Fig 7A). Yet, these reactions are the most common drug allergic events in human medicine.\textsuperscript{3,8,43-48} Importantly, 40.5\% of the clinical signs listed by the respondents are characteristic of dose-dependent type A ADR (e.g. vomiting, ataxia) and are rarely seen with
drug allergy (Fig 7B). These results illustrate that a significant number of veterinarians confused dose-dependent direct drug toxicity and drug allergy, and that the majority of responders mainly (if not even exclusively for some of them) consider immediate reactions when thinking about drug allergy.

This could be the consequence of the lack of training reported by our participants. This could lead to a significant risk of misdiagnosing these reactions\(^{22,28,49}\) and poorer outcome,\(^{16,17}\) as previously shown in human medicine.

At the end of the survey, 79.4% of the 252 participants expressed the desire to learn more about drug allergy. This support the participants’ opinion at the beginning of the survey, that they felt inadequately prepared to recognize and treat drug allergic reactions.
CONCLUSION

For the first time in veterinary medicine to our knowledge, veterinarians were surveyed about their awareness on the subject of drug allergy. The results of this survey suggest a lack of awareness and/or knowledge about drug allergic reactions amongst veterinarians. Our data further suggests a lack of training in veterinary medical school and a lack of information in the literature about veterinary drug allergy. Importantly, the survey also highlights the interest of the participants to learn more on the subject. Yet, a larger survey will be required in order to confirm and refine these suggested conclusions. Such survey would include veterinarians from different US veterinary schools with refined questions based on weaknesses discovered when analyzing this pilot survey.
ACKNOWLEDGMENTS

I want to thank Dr. Marilyn O’Hara for her advice in the early stage of the survey organization, Misty Oakley (UIUC veterinary medicine Alumni office) for her help in contacting the UIUC alumni, and the persons who Beta-tested her survey. Finally, I would like to thank Dr David Schaeffer for his assistance in analyzing the more complex aspect of our survey answer profile.
Table II: Categories of clinical signs that responders associate with drug allergy

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin &amp; mucosal skin junctions</td>
<td>472 (44.7%)</td>
</tr>
<tr>
<td>GI</td>
<td>312 (29.5%)</td>
</tr>
<tr>
<td>Behavior and neurological system</td>
<td>85 (8.0%)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>58 (5.5%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>54 (5.1%)</td>
</tr>
<tr>
<td>Fever</td>
<td>32 (3.0%)</td>
</tr>
<tr>
<td>Blood cell abnormalities</td>
<td>14 (1.3%)</td>
</tr>
<tr>
<td>Eyes</td>
<td>8 (0.8%)</td>
</tr>
<tr>
<td>Liver</td>
<td>7 (0.7%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>5 (0.5%)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (0.5%)</td>
</tr>
<tr>
<td>Joints</td>
<td>4 (0.4%)</td>
</tr>
</tbody>
</table>
Table III: Details of all the clinical signs affecting the skin and mucocutaenous junctions (including ears and eyes)

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>urticaria, hives, severe hives, mild hives, wheals, rashes, skin rash</td>
<td>175 (37.1%)</td>
</tr>
<tr>
<td>angioedema, swollen face, swelling of face/muzzle, facial edema, angioneurotic edema, facial swelling, subcutaneous edema, swollen muzzle, swelling</td>
<td>93 (19.7%)</td>
</tr>
<tr>
<td>pruritus, prurit</td>
<td>43 (9.1%)</td>
</tr>
<tr>
<td>skin/cutaneous reaction, skin/cutaneous/dermatological lesions, skin/dermatologic change/action, dermatologic/dermatological manifestation, dermatopathy, dermatologic evidence, cutaneous/derm signs, skin problem/disorder, abnormal skin, skin manifestation</td>
<td>41 (8.7%)</td>
</tr>
<tr>
<td>erythema, severe erythema, erythema of skin, skin erythema, skin redness, annular erythemic lesions</td>
<td>22 (4.7%)</td>
</tr>
<tr>
<td>papule, vesicule, skin eruption</td>
<td>21 (4.4%)</td>
</tr>
<tr>
<td>itching, itch, itchiness</td>
<td>17 (1.5%)</td>
</tr>
<tr>
<td>steven Johnson syndrome, toxic epidermal necrolysis, sloughing of the skin, sloughing tissue, peeling of the skin, skin necrosis, erythema multiforme, mucosal sloughing</td>
<td>15 (1.0%)</td>
</tr>
<tr>
<td>vasculitis</td>
<td>8 (1.7%)</td>
</tr>
<tr>
<td>dermatitis/ skin inflammation</td>
<td>8 (1.7%)</td>
</tr>
<tr>
<td>contact reaction, local dermatological reaction if topical medication,</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td>Condition</td>
<td>Count (%)</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>injection site reaction/inflammation, contact allergy, local reaction of administration site</td>
<td></td>
</tr>
<tr>
<td>dry eyes, decrease tears production, kcs</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td>conjonctival erythema, conjunctival hyperemia, red eyes, peri-ocular blepharitis, peri-ocular dermatitis, peri-ocular swelling</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td>Skin/dermal ulceration, oral ulceration</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td>alopecia/hair loss</td>
<td>5 (1.1%)</td>
</tr>
</tbody>
</table>
Table IV: Details of digestive signs (including the liver)

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>n  (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vomiting, nausea</td>
<td>140 (44.9%)</td>
</tr>
<tr>
<td>diarrhea, colic</td>
<td>113 (36.2%)</td>
</tr>
<tr>
<td>gastro-intestinal signs/issues/upset/disturbance/symptoms</td>
<td>32 (10.3%)</td>
</tr>
<tr>
<td>anorexia, inappetence, decrease appetite, lack of appetite</td>
<td>19 (6.1%)</td>
</tr>
<tr>
<td>hepatopathy, liver, hepatic necrosis, increase liver enzymes, liver failure,</td>
<td>8 (2.6%)</td>
</tr>
<tr>
<td>liver reaction</td>
<td></td>
</tr>
</tbody>
</table>
Table V: Details of behavioural and neurological signs

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lethargy, depression, weakness, malaise</td>
<td>42 (49.4%)</td>
</tr>
<tr>
<td>neuro signs, neurologic, neurological manifestation, neuro problem</td>
<td>17 (20.0%)</td>
</tr>
<tr>
<td>seizure, tremor, trembling, muscle tremor, jerky movements, ataxia</td>
<td>11 (12.9%)</td>
</tr>
<tr>
<td>behavioral changes</td>
<td>5 (5.9%)</td>
</tr>
<tr>
<td>hyperactivity, hyperexcitability, agitation, anxiety, restlessness</td>
<td>5 (5.9%)</td>
</tr>
<tr>
<td>ataxia</td>
<td>5 (5.9%)</td>
</tr>
</tbody>
</table>
Table VI: Details of respiratory signs

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>respiratory distress, dyspnea, trouble breathing, respiratory difficulties</td>
<td>42 (72.4%)</td>
</tr>
<tr>
<td>labored respiration, difficulty breathing</td>
<td></td>
</tr>
<tr>
<td>respiratory/respiratory signs, respiratory abnormalities</td>
<td>6 (10.3%)</td>
</tr>
<tr>
<td>tachypnea/rapid respiration</td>
<td>5 (8.6%)</td>
</tr>
<tr>
<td>swelling airways, laryngeal edema, pharyngeal edema, swelling of the pharynx</td>
<td>5 (8.6%)</td>
</tr>
<tr>
<td>larynx, tongue swelling</td>
<td></td>
</tr>
</tbody>
</table>
Table VII: Details of cardiovascular signs

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>collapse, acute collapse, circulatory collapse, cardiovascular collapse</td>
<td>15 (27.8%)</td>
</tr>
<tr>
<td>hypotension, paleness, pales mucous membranes, palor</td>
<td>15 (27.8%)</td>
</tr>
<tr>
<td>shock, anaphylactic shock</td>
<td>8 (14.8%)</td>
</tr>
<tr>
<td>Tachycardia, bradycardia</td>
<td>6 (11.1%)</td>
</tr>
</tbody>
</table>
Table VIII: Biochemistry abnormalities associated with drug allergic reaction by the responders.

<table>
<thead>
<tr>
<th>Blood work abnormalities</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>73 (54.9%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>25 (18.8%)</td>
</tr>
<tr>
<td>Proteins (Total Protein, albumin and globulines)</td>
<td>16 (4.5%)</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>7 (5.3%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Glycemia</td>
<td>3 (2.3%)</td>
</tr>
<tr>
<td>Blood gases</td>
<td>3 (2.3%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2 (1.5%)</td>
</tr>
</tbody>
</table>
Table IX: Blood cell count abnormalities (n=158)

<table>
<thead>
<tr>
<th>Blood cell lines</th>
<th>n (%)</th>
<th>Abnormalities Answers</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>65 (24.7%)</td>
<td>Decrease</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not specified</td>
<td>4</td>
</tr>
<tr>
<td>Platelets</td>
<td>32 (12.2%)</td>
<td>Decrease</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not specified</td>
<td>2</td>
</tr>
<tr>
<td>White blood cells</td>
<td>69 (26.2%)</td>
<td>Decrease</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not specified</td>
<td>21</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>75 (28.5%)</td>
<td>Increase</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not specified</td>
<td>2</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>14 (5.3%)</td>
<td>Decrease</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase</td>
<td>12</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>3 (1.1%)</td>
<td>Decrease</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase</td>
<td>1</td>
</tr>
<tr>
<td>Basophils</td>
<td>2 (0.8%)</td>
<td>Increase</td>
<td>2</td>
</tr>
<tr>
<td>Mast cells</td>
<td>1 (0.4%)</td>
<td>Increase</td>
<td>1</td>
</tr>
<tr>
<td>Monocytes</td>
<td>1 (0.4%)</td>
<td>Increase</td>
<td>1</td>
</tr>
</tbody>
</table>
Table X: Reason why the veterinarian did not take the survey.

<table>
<thead>
<tr>
<th>Reasons why the survey was not completed</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lack of time</td>
<td>8 (28.6%)</td>
</tr>
<tr>
<td>nothing to say about the topic</td>
<td>9 (32.1%)</td>
</tr>
<tr>
<td>missed the emails</td>
<td>3 (10.7%)</td>
</tr>
<tr>
<td>no interest on the topic</td>
<td>1 (3.6%)</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

Figure 2: Professional training level of the responders.

Panel A presents the distribution of board training and/or certification, and panel B of research training and degrees, among the survey participants.

A. Board training or certification  (*see acronyms in appendix*)

B. Research training or degree
Figure 3: Rough estimate of drug allergy incidence in the responder’s practice.
Figure 4: Inquiring for previous history of drug allergic reaction while taking the history of the patients.
Figure 5: Warning about the risk of allergic drug reaction when prescribing medication.
Figure 6: Frequency of “drug allergy” inclusion into the differential diagnosis.
Figure 7: Types of reaction describe by the clinical signs given by the responders.

Panel A presents the percentage of clinical signs given by the responders that can be associated with immediate or delayed drug allergic reactions. Panel B presents the categories of clinical signs associated with drug allergic reactions by the responders.

A. Type of reaction per responders

B. Type of reaction for all the clinic signs
Figure 8: Organ systems associated with drug allergic reactions by the responders.
REFERENCE LIST


ABSTRACT

Drug allergic/hypersensitivity reactions are antigen-specific immune-mediated adverse drug reactions. They can be immediate (IgE-mediated) or delayed (IgG- or T cell-mediated). In human medicine, they are estimated to affect 0.1-3% of the general population and up to 7% of hospitalized patients. The dog has been proposed as a potential animal model to study drug HS. Indeed, drug hypersensitivity reactions appear similar clinically in dogs and humans, but their exact incidence in dogs remains unknown. Therefore, his retrospective study aimed to estimate the incidence and characterize drug HS reactions in dogs seen at the state veterinary teaching hospital during the past 11 years. We conducted a tiered keyword search of the two clinical medical databases and thoroughly reviewed identified cases of potential drug HS. This approach led to 65 cases (1 immediate and 55 delayed reactions), suggesting an incidence of 0.15%. The suspected drug was an antibiotic in 58.4% cases, an antiparasitic in 43.1% cases, an NSAID in 12.3% cases, a barbiturate in 10.8% cases, and an opioid in 10.8% cases, but 46.9% of these dogs were on multiple drugs at the time of the reaction. Delayed reactions involved the skin (61.8%), blood cells (47.3%), or the liver (23.6%), but multiple organs were affected in 32.7% cases. Hospitalization was required in 30% (n=3) of immediate reactions and lasted from 12 to 48 hours in these case (median 24 hour); none of these patients died from their drug allergic reaction. Hospitalization was required in 42.3% (n=26) of the delayed reactions, with a duration that ranged from 12 hours to 12 days (median 3.0 days) Eight cases (14.5%) did not survive their
drug allergic reaction, all of which were delayed reactions. Three patients (with delayed reactions) were maintained on the drug after a drug allergic reaction had been suspected. The state of all 3 patients worsened, eventually leading to the dogs’ euthanasia. 19 cases matched the definition of DRESS (Acronym of Drug Rash with Eosinophilia and Systemic Symptoms) and five cases matched the definition of allergic contact dermatitis.
INTRODUCTION

Adverse Drug Reactions (ADR) can be classified into Type A (dose dependent, predictable, and directly related to pharmacology/chemical properties) and Type B reactions (not dose dependent, non-predictable). Immune-mediated Type B reactions are called “drug hypersensitivity” or “drug allergy”, and can be categorized into immediate (anaphylactic) or delayed reactions.\(^1\)\(^{-}\)\(^8\) In human medicine, drug hypersensitivity reactions are thought to account for 1/3 of all ADRs and are thought to affect 0.2 - 3\% for the general patient population, and potentially up to 15-20\% of hospitalized patients.\(^9\)\(^{-}\)\(^{15}\) In veterinary medicine, the incidence of drug allergic reactions is unknown amongst species.

A drug allergic reaction requires the sensitization of the immune system against the culprit drug, which represents the antigen in this immune reaction. A period of minimum 4-5 days is required for the immune system to mount a response against a new antigen. This is why delayed reactions required at least 4-5 days of drug exposure before the onset of clinical signs, unless the patients was previously exposed to the drug.\(^{16}\)\(^{,}\)\(^{17}\) Immediate drug allergic reactions occur within 24 hours of drug exposure, usually 1 to 2 hours, but the original sensitization required several days of exposure or repeated exposure prior to the first episode of reaction. Clinical presentations of such immediate reactions usually include cutaneous signs, such as urticaria or angioedema, bronchospasm, and sometimes vomiting, diarrhea or cardiovascular shock. Anaphylactic drug reactions can be life threatening when they obstruct airways or lead to an anaphylactic shock.

Clinical signs observed during “delayed” drug allergy commonly involve the skin,\(^6\)\(^,\)\(^{17}\)\(^{-}\)\(^{20}\) with clinical signs as mild as a rash but potentially very severe such as Stevens-Johnson
Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) which carry a 10-50% risk of death even in modern human medicine. Blood cells are also common targets of delayed drug allergy: e.g. immune-mediated haemolytic anemia (IMHA), immune-mediated thrombocytopenia ("ITP"), or life-threatening pancytopenia. The liver can also be affected, sometimes leading to life-threatening hepatitis.

In any case, the diagnosis of drug allergic reactions is mainly based on clinical presentation and recent exposure to a drug. Drug challenges can also be used as diagnostic tool and they are considered as very reliable. A dechallenge consists in interrupting the administration of the suspected drug to see whether the clinical signs resolve. Afterwards, a rechallenge can be attempted by reintroducing the drug. If the clinical signs reoccur a drug allergy is highly suspicious. However, rechallenges can trigger life threatening reactions and are therefore not commonly recommended. Yet, these rechallenges can sometimes be performed involuntarily during the course of the patient therapy and the thorough review of the therapeutic history is primordial.

The use of algorithms in diagnosing ADRs has been described in human medicine. These algorithms are more easily used for type A reactions where clinical signs of direct toxicity have already been clearly established. However, these algorithms can be applied to drug allergic reactions as well. More recently, specific algorithms have been established for drug allergic reactions. They put more emphasis on the history of the patient (e.g. timing, previous exposure), results of diagnostic tests more specific to immune-mediated reactions (skin prick test, skin intradermal test), and provocation tests ("rechallenges").

The discontinuation of the culprit drug is thekeystone component of the treatment. Supportive care is sometimes needed with certain clinical presentations: e.g. topical treatment
with open skin lesions; blood transfusion with anemia; antihistamines with urticarial; or IV fluids with shock. The prognosis will depend a lot on the early recognition of the reaction, the early withdrawal of the drug, and the reaction’s target organ.31

Our primary goal was to estimate the incidence of drug allergic reactions in dogs seen at the University of Illinois veterinary teaching hospital, using its medical archives. We also aimed to further characterize these drug allergic reactions: drugs involved clinical pattern, diagnosis, management, outcome, and reporting.
METHODS

Search approach

We searched two electronic databases of the UIUC veterinary teaching hospital (VTH): VetStar that is used to archive medical record documents; VAD that is more specifically used by the diagnostic laboratory to archive laboratory results. Both databases were searched for dog cases in the period of January 1\textsuperscript{st} 2003 till April 28\textsuperscript{th} 2014 (approximately 11 years).

These searches were based on a 3 tier-keyword approach. In tier 1, we used keywords that are specific to drug allergy: drug hypersensitivity, drug allergy, drug allergic reaction, adverse drug events/reactions, drug reaction, and adverse reaction. In tier 2, we used clinical terms that are commonly associated with drug allergy, but also with other pathologies: anaphylaxis, anaphylactic reaction/shock, angioedema, urticaria, Erythema Multiforme, Steven-Johnson syndrome, Toxic Epidermal Necrolysis, face swelling, swollen face, nose swelling, and swollen nose. Finally, tier 3 terms included clinical descriptors where drug allergy is a possible, but not frequent diagnosis: arthropathy, polyarthropathy, IMHA, ITP, Evens syndrome, aplastic anemia, autoimmune disease, discoid lupus erythematos, and lupus erythematos. Additionally, the searches in VAD included some keywords that were more specific to laboratory diagnostic tests (Table I): e.g. lymphopenia for complete blood count; eosinophilic hepatitis or immune-mediated nephritis for organ biopsy and cytology. Finally, we also investigated 30 specific VTH cases for which Dr. Lavergne had been consulted during the previous 5 years because of a suspicion of drug allergic reaction. The 3 lists of cases were then merged and the duplicates were removed.

Exclusion criteria
We excluded the cases with medical records on microfilms. We did not include patients that had a history of drug allergy, but were not treated for it the VTH. We excluded cases where a diagnosis different than drug allergy was confirmed beyond reasonable doubt. Finally, we eliminated cases where the lack of information in the medical record prevented from applying a reliable reasoning on the likelihood of a drug allergic reaction.

Inclusion criteria

To be included in the study, the following criteria had to be met: The patient had to be on the drug for more than 5 days before the reactions, if less than 5 days, the patient had to have a previous exposure to the drug. The clinical signs had to be compatible with an immune reaction. The clinical signs resolved when the drug is discontinued (dechallenge) and/or reoccur when the patient was put back on the drug (rechallenge).

Likelihood of a drug allergic reaction

The likelihood of the drug allergic reaction was categorized as “likely” or “possible”. A case was considered “likely” if clinical and circumstantial evidence pointed towards drug allergy as the most likely diagnosis. A case was considered “possible” when the available information supported the possibility of a drug allergic reaction without eliminating other etiologies.

DRESS cases (“Drug Rash with Eosinophilia and Systemic Symptoms”)

The DRESS syndrome is a severe form of systemic delayed drug allergy with a wide range of clinical presentations. The clinical signs can include fever (can be marked), skin lesions (often start as a rash), lymphadenopathy, eosinophilia, and internal organ dysfunction (often the
liver).\textsuperscript{32,33} We used a modified RegiSCAR scale\textsuperscript{34} to identify DRESS cases among our cohort. To be included in this category, the case had to match at least 3 of the 5 following criteria: 1) suspected immune-mediated drug reaction, 2) skin lesions, that initially started with a rash 3) fever, 4) systemic involvement including internal organs (e.g. adenopathy, hepatitis, nephritis) or peripheral lymphadenopathy, and/or 5) blood cell count abnormalities.

Allergic Contact Dermatitis

Allergic contact dermatitis is an allergic reaction to a drug administered topically on the skin.\textsuperscript{35-38} These reactions are limited to the skin, and can be extensive.

Statistical analysis

Descriptive statistics were used to summarize the data: mean and standard deviation or median and range.
RESULTS

Case attrition via the step-by-step review process (Fig. 9)

When combining the search lists from the VTH, VDL and consulting cases, 25,127 medical numbers where collected. After removal of all the duplicates, a total of 11,643 cases were left for review. The first screening aimed to eliminate cases not relevant for our study. Indeed, due to the unspecific keywords (tiers 3) for the searches, cases unrelated were present in the listing. For example, when using facial swelling for the search, a majority of facial trauma and dentistry cases were identified. Also, the services of dentistry, orthopedic surgery, oncology, and primary care, include a general warning for drug allergic reaction in their discharge letter. At end of the first screening, 2000 cases were selected for an in depth review by a veterinarian to eliminate cases based on the previously described inclusion and exclusion criteria. The remaining 106 potential cases were then reviewed by a specialist in drug allergy to determine the likelihood of the drug allergic reaction. Sixty-five cases were finally selected for our detailed analysis and further characterization.

Incidence

During our study period (≈11 years), 44,531 dogs were seen at the UIUC VTH and we identified 65 “likely” or “possible” cases of drug allergy. This would estimate the incidence of drug allergic reactions around 0.15%.

Amongst the 65 cases, 55 were “delayed” reactions (83.3%). Amongst the 55 delayed reactions, 43 were categorized has likely (78.2%) and 12 as possible (21.8%). For 83.7% of the former cases, a drug allergy was suspected or discussed in the medical record. A differential
The diagnosis was not found in the chart 61.5% of the cases. For 41.7% of the latter cases, a drug allergy was suspected or discussed in the medical record. Eleven of the 66 identified cases were “immediate” reactions (16.7%). Amongst these 10 cases, 5 were categorized as “likely” (50%) and 5 as “possible” (50%). For 60% of the former cases, a drug allergy was suspected or discussed in the medical record. For none of the latter cases, a drug allergy was suspected or discussed in the medical record.

Case population description (Table XII)

The gender ratio in our selected cases was 1:1. The most common breeds were mixed breed dog (26.2%), labrador retriever (10.8%), shih tzu (6.2%), american pit bull terrier (4.6%), maltese (4.6%), pug (4.6%), shetland sheepdog (4.6%), chihuahua (3.1%), cocker spaniel (3.1%), german shepherd dog (3.1%), pomeranian (3.1%), and vizsla (3.1%).

Onset of the reaction

The time between when the suspected drug was first started and the onset of the clinical signs was clearly established for 23 cases (35.4%; 4 immediate and 29 delayed reactions).

The onset ranged from 1 to 5 hours (median 1.5 hour) for immediate reactions and from 1 day to 44 months (median 7 days) for delayed reactions. Importantly, the 5 patients affected by a delayed drug allergy that started less than 5 days after drug exposure started, had been exposed to the culprit drug previously. Interestingly, the median onset was 8 months (4 days-44 months) for phenobarbital. For 42 cases (64.6%; 6 immediate and 26 delayed reactions), we could not establish the delay between first drug dose and reaction onset beyond the fact that the animal had been receiving the medication for at least 5 days.
Clinical presentation

Amongst the immediate reactions, 90% involved the skin (Fig 10-A). The remaining case involved the gastrointestinal and cardiovascular system. The most frequent cutaneous signs amongst these reactions were urticaria (50.0%), angioedema (50.0%), and pruritus (20.0%). Thirty% of these patients displayed a combination of 2 or 3 clinical signs (e.g. urticaria and angioedema; urticaria, angioedema, and pruritus).

Amongst the delayed reactions, the organ system that was the most commonly affected was the skin (61.8%), followed by blood cells (47.3%), and the liver (23.6%) (Fig 10-B1). The two most commonly affected blood cell lines were red blood cells (34.6% of cases with blood dyscrasias) and platelets (12.8%). Blood dyscrasia affecting all blood cell lines (pancytopenia, aplastic anemia) represented 5.5% of blood cell cases (Fig 10-B2). Multiple organs were affected in 32.7% of the delayed reactions: skin & blood (2 cases); skin & liver (3 cases); blood & liver (4 cases); skin & blood & liver (5 cases).

Severity of the reactions

Hospitalization was required in 30% (n=3) of immediate reactions and lasted from 12 to 48 hours in these case (median 24 hour) (Table XIII). Two of these patients were in shock at presentation and all had cutaneous signs. Importantly, none of these patients died from their drug allergic reaction.

Hospitalization was required in 42.3% (n=26) of the delayed reactions, with a duration that ranged from 12 hours to 12 days (median 3.0 days) (Table XIII). Amongst these hospitalization, clinical signs involved blood cell lines in 34.5% of cases, the skin in 10.9% of
cases, and the liver in 9.0% of cases. Eight cases (14.5%) did not survive their drug allergic reaction, all of which were delayed reactions. Six were euthanized (75%) and 2 (25%) died naturally. Seven of these patients had required to be hospitalized (87.5%). In the survivor group, 48.9% were characterized as “improved” in the discharge, 31.9% as “unchanged”, and there was no information about the patient’s status at discharge in 19.2% unknown (14.9% “undetermined” status option in the discharge and 4.3% without any information available).

Interestingly, three patients (with delayed reactions) were maintained on the drug after a drug allergic reaction had been suspected. The state of all 3 patients worsened, eventually leading to the dogs’ euthanasia.

Suspected drugs
Almost half of the patients (46.9 %) were on multiple drugs when they developed their drug allergic reaction. The classes of drug suspected for all the reactions included are detailed in Tables XIV. The main classes of drug suspected for the delayed reactions include antibiotics (55.5%), antiparasitics (41.8%), non-steroidal anti-inflammatory (12.7%), topicals (12.7%), steroids (12.7%), barbiturics (12.7%), H1 antagonists (7.3%), opioids (5.4%), thyroid supplements (3.6%), azole antifungals (3.6%), antiemetics (3.6%), and ears medication (3.6%).

DRESS cases
Nineteen cases matched the criteria of DRESS (34.5% of delayed reactions). The estimated incidence is 0.04%. Table II and III compare the characteristics of these patients with the other cases. Almost half these patients (47.4%) required a hospitalization. Table IV indicates the drugs involved in these cases. Amongst these 19 DRESS cases, 68.4% were categorized as “likely” and
31.6% as “possible”. The possibility of a drug allergy was discussed in the medical record in 92.3% of the “likely” DRESS cases, and 50% of the “possible” ones. One patient was kept on the drug suspected being the trigger of the reaction; the same patient did not survive. The timing between the beginning of medication and the reaction was identifiable for 52.6% of the DRESS cases, ranging from 2 days to 1 year (median 4.5 days).

**Allergic Contact Dermatitis**

Amongst the delayed reactions, 5 cases matched the definition of allergic contact dermatitis (4 “likely” and 1 “possible”). The estimated incidence is of 0.01%. Table I compares the characteristics of these patients with the other cases. No hospitalization was required in these and they all survived the drug reaction. All the drug suspected in these contact dermatitis cases were topical flea and tick preventatives (Table XIV). For 100% of the “likely” contact dermatitis identified, a drug allergy was discussed in the medical record. For the “possible” case, a drug allergy was not suspected.
DISCUSSION

The goal of our study was to estimate the incidence of drug allergic reaction amongst the dog population seen at the VTH. We were also interested in characterizing the clinical pattern (timing, clinical signs, severity, and outcome) and the suspected drugs.

The incidence of 0.15% we found in our study is in the lower range of what has been reported in human medicine.\textsuperscript{9-11} This was the first attempt at estimating the incidence of drug allergy in veterinary medicine that did not focus on one given class of drug. Governmental reporting systems have never reported on drug allergic reactions either. Thus, we cannot compare our incidence to any previous reports. However, we suspect that it is underestimated, mainly due to the lack of awareness from clinicians often associated with a lack of important information in the medical record to allow for suspect cases to be included. It is important to note that the dogs seen at our veterinary teaching hospital are not frequently hospitalized. So the real incidence of drug allergy in our dog patients should not be compared to the incidence reported in human hospitals.

Interestingly, we reviewed in depth approximately 2000 potential cases, but about 40% of the cases had to be put aside because some key information was missing. A thorough review of the past history is critical to diagnosis a drug allergy. Some cases had only a partial medical history with the VTH, and the chart of the referral veterinarian was not always available. When available, these charts were not always complete or given enough information on the clinical signs or medication (name of the drug, dosage). Some of them were also not readable due to the handwriting. Importantly, the VTH medical records themselves often lacked important elements, especially when the clinician had not included drug allergy in his/her differential diagnosis,
Despite the fact that multiple elements in the patient’s history and/or its clinical presentation were compatible with such ADR. In human medicine it has been clearly demonstrated that the lack of completeness and quality of the patient’s chart lead to preventable medical errors.\textsuperscript{39}

The exact timing between the onset of the reaction and when the drug was originally started was not always identified clearly in the medical record, and we were only able to calculate this onset for 58.5\% of our patients (34 delayed and 4 immediate reactions). Often the suspected drug was started by the referral veterinarian who did not provide any timing information or his/her notes were not readable. Of the onsets of immediate reactions we were able to calculate, the median of 1.5 hours. The onsets we were able to calculate matched those reported in human medicine.\textsuperscript{16,17} Interestingly, the median delay for the phenobarbital was longer (8 months) like describe in human medicine. Phenobarbital has a much longer half-life than most drugs, which delays drug accumulation in patients and could explain the longer period of time before the onset of a drug allergic reaction. Two cases with phenobarbital allergy exhibited clinical signs compatible with a DRESS reaction, which is often associated with a very long delay onset in human medicine.\textsuperscript{40}

In our study, immediate drug allergic reaction represented approximately 15 \% of our cases compared to 30-40\% in human medicine.\textsuperscript{9-15} This discrepancy could represent a true difference between dogs and humans. However, we suspect that the proportion of immediate reactions was underestimated. Indeed, most medical records of patients seen for anaphylaxis have an extremely limited history and do not include any etiology. The exact incidence of anaphylaxis in dogs as well as the prevalence of each etiology (insects, plants, drugs, vaccines, food) has not yet been studied.\textsuperscript{41} However, an unpublished investigation from our group has been able to estimate an incidence of 1.3\% of anaphylactic reactions at our teaching hospital over a
similar period to the one used in the present retrospective study. This unpublished investigation on anaphylaxis included 10.4% of anaphylaxis linked to a drug, 33.3% to a vaccine, 13.5% to insects, 5.2% to other chemicals or material exposure, and 37.5% without known etiology.

As previously described in human medicine, antibiotics (57.6%) and NSAIDs (12.1%) were the most commonly suspected drug classes in our study (Table XIV). These two classes of drugs are the most commonly used in human and veterinary medicine. This could explain the higher percentage of reactions. We also showed that antiparasitic drugs were commonly associated with drug allergic reactions in our dogs (42.4%). Many dogs receive prophylactic antiparasitic therapy on a monthly basis, and this could explain why these drugs take the second place before NSAIDs if compared with humans. This cannot be directly compared with the situation in human medicine as antiparasitics are not commonly used in humans, especially not in western countries. As in human medicine, barbiturics and opioids were also implicated in many of our cases (10.8% for each).

To the best of our knowledge, we are the first to report some cases of DRESS in veterinary medicine. Our study estimated an incidence of 0.04% for DRESS. This would be within the range reported for DRESS in human medicine: 1 case for 1000 or 10,000 of drug exposure (0.01-0.1%). The mortality rate amongst our DRESS cases was 5%, which matches the lower end of the range found in human cases (5-20%). It is important to note that we identified our cases of DRESS using criteria established in human medicine. These criteria may not be directly adaptable to DRESS in dogs. Future work will be required to further characterize this syndrome in dogs. The median of 4.5 days for the onset of the reaction after the medication was started, is lower than the 7-12 days described in human medicine.
Also, to the best of our knowledge, the incidence of contact dermatitis in general remains undetermined in veterinary medicine. We are the first to report an incidence for contact allergic dermatitis associated with drugs in dogs. It is important to note that the common usage of spot-on preventative drugs in dogs may impact the frequency of drug contact dermatitis compared to what is observed in humans, but its incidence in human medicine remains to be established as well. Our data confirm what has been discussed in veterinary review articles, in that, our drug-induced contact dermatitis were mild and carried out a good prognosis. Therefore, these cases are less likely to be seen by a tertiary referral hospital, such as ours, and the incidence of drug allergic contact dermatitis might be higher in general private practice.
CONCLUSION

This study is the first to estimate an incidence for drug allergic reaction in dogs, as the first to report cases of DRESS in dogs, and the first to establish an incidence for drug allergic contact dermatitis. The incidence, the clinical pattern, and the drugs involved matched what has been described in human medicine. This study also demonstrated a link between early drug discontinuation and prognosis as shown in human drug allergy that has already been demonstrated in human medicine. The quality and completeness of the medical record were important limiting factors. We hope that this study will raise awareness about the risk of drug allergy in dogs, but also on the importance of record keeping for both the patient and science.
ACKNOWLEDGMENTS

I would like to thank Natalie Laskowski, Dianna Clark and Arthur Siegel who helped with the search for medical records, as well and Ryan Hanna, Karen Allen and Marie Childress who helped with the search in the VDL database. I finally thank Cassandra Wolsic, Audrey Billhymer, and Julia Schimansky for their help collecting some data out of certain records.
TABLE XI: Categories of keywords used for the VDL search

<table>
<thead>
<tr>
<th>Keyword</th>
<th>Number of cases found</th>
</tr>
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<tr>
<td>General</td>
<td>47</td>
</tr>
<tr>
<td>Liver</td>
<td>641</td>
</tr>
<tr>
<td>Kidney</td>
<td>1364</td>
</tr>
<tr>
<td>Musculoskeletal</td>
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<tr>
<td>Respiratory</td>
<td>378</td>
</tr>
<tr>
<td>Ocular</td>
<td>231</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>223</td>
</tr>
<tr>
<td>Bone Marrow / blood</td>
<td>518</td>
</tr>
<tr>
<td>Skin &amp; mucocutaneous junction</td>
<td>1305</td>
</tr>
<tr>
<td>CNS</td>
<td>209</td>
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<tr>
<td>Miscellaneous</td>
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<td>Total (with duplicates)</td>
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<td>-----</td>
<td>-------</td>
</tr>
<tr>
<td>Total</td>
<td>2328</td>
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Table XII: Case population description

<table>
<thead>
<tr>
<th></th>
<th>Immediate reactions</th>
<th>Delayed reactions</th>
<th>DRESS</th>
<th>Allergic Contact Dermatitis</th>
<th>All reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male: female</td>
<td>7:4</td>
<td>26:29</td>
<td>8:11</td>
<td>4:1</td>
</tr>
<tr>
<td>Age (year, month)</td>
<td>Median</td>
<td>2y (4m-8y11m)</td>
<td>6y 5m (10m-13y1m)</td>
<td>8y 4m (2y-12y)</td>
<td>1y 6m (7m-10y7m)</td>
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<tr>
<td></td>
<td>Weight (kg)</td>
<td>Median 23.2 (7-35.4)</td>
<td>20.2 (2.7-60.5)</td>
<td>17.6 (3.7-40.30)</td>
<td>35.7 (8-60.5)</td>
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</table>
Table XIII: Hospitalizations

<table>
<thead>
<tr>
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<th>Immediate reactions</th>
<th>Delayed reactions</th>
<th>DRESS</th>
<th>Allergic Contact Dermatitis</th>
<th>All reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of hospitalized animals</td>
<td>36.4</td>
<td>47.3</td>
<td>47.4</td>
<td>0</td>
<td>45.5</td>
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<tr>
<td>Hospitalization Duration (days)</td>
<td>Median (range)</td>
<td>0.75 (0.5-2)</td>
<td>3 (0.5-12)</td>
<td>3 (0.5-12)</td>
<td>0 (0.5-12)</td>
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</table>
# Table XIV: Suspected drugs

<table>
<thead>
<tr>
<th>Drug classes</th>
<th>Details</th>
<th>Immediate reactions n (%)</th>
<th>Delayed reactions n (%)</th>
<th>DRESS n (%)</th>
<th>Allergic Allergic Contact Dermatitis n (%)</th>
<th>All reactions n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td>11 (16.7)</td>
<td>55 (83.3)</td>
<td>19 (28.8)</td>
<td>5 (7.6)</td>
<td>65 (100)</td>
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<td>Antibiotics</td>
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<tr>
<td>Cephalosporins</td>
<td>3 (27.3)</td>
<td>34 (54.5)</td>
<td>10 (52.6)</td>
<td>38 (58.4)</td>
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<td>Cephalosporins</td>
<td>2</td>
<td>14</td>
<td>1</td>
<td>16 (42.1)</td>
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<td>Cephalexin</td>
<td>1</td>
<td>1</td>
<td>10</td>
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<td>Cefpodoxime</td>
<td>1</td>
<td>6</td>
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<td>Beta-lactam</td>
<td>10</td>
<td>5</td>
<td>10 (26.3)</td>
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<td>Amoxicillin/Clavulanic Acid</td>
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<tr>
<td>Amoxicillin/Sulbactam</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Penicillin</td>
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<td>2</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Amoxicillin</td>
<td>1</td>
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<tr>
<td>Sulfonamides</td>
<td>4</td>
<td></td>
<td></td>
<td>4 (10.5)</td>
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<tr>
<td>Ormetoprin/Sulfadimethoxine</td>
<td>1</td>
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<tr>
<td>Trimethoprim/Sulfadiazine</td>
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<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>1</td>
<td></td>
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</tr>
<tr>
<td>Class</td>
<td>Unknown Sulfa</td>
<td>Nitroimidazoles</td>
<td>Metrinodazole</td>
<td>Quinolones</td>
<td>Enrofloxacin</td>
<td>Ciprofloxacin</td>
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<td>----------------------------</td>
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<td>---------------</td>
<td>------------</td>
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<td></td>
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<td>1</td>
<td>3</td>
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<td>4 (10.5)</td>
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<table>
<thead>
<tr>
<th>Antiparasitics</th>
<th>4 (36.6)</th>
<th>23 (41.8)</th>
<th>2 (10.5)</th>
<th>5 (100)</th>
<th>28 (43.1)</th>
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</thead>
<tbody>
<tr>
<td>Ivermectin/Pyrantel Pamoate</td>
<td>1</td>
<td>6</td>
<td>7</td>
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<td>(1.8)</td>
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Figure 9: Case attrition during the review process
Figure 10: Clinical signs involved with cases of drug allergy

Panel A presents the clinical signs observed in patients who suffered from an immediate drug allergic reaction among our cohort. Panel B focuses on delayed reactions, with B.1 presenting organ systems involved and B.2 the types of blood dyscrasia.
A. Clinical signs associated with immediate reactions

B. Clinical signs involved with delayed reactions

B.1. Organ systems

B.2. Types of blood cell dyscrasia
REFERENCE LIST


The World Health Organization defines adverse drug reactions (ADRs) as “noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment”. These ADRs can be classified under two types of events. Type A reactions (60-80%) are dose dependent, predictable, and directly related to pharmacology/chemical properties. Type B reactions (20-40%) are not dose dependent, non-predictable, and if immune-mediated are called “drug hypersensitivity” or “drug allergy”. These later reactions are further separated into two categories: immediate (anaphylactic) or delayed reactions.

In human medicine, adverse drug reactions in general are the 4th-6th cause of death. They affect 10-20% of the hospitalized patients and 7% of general population. The annual cost of these reactions, including treatment of the primary reactions, complications, and increased length of hospitalization is estimate to $500 billion in the United States.

Drug hypersensitivity reactions are thought to account for 1/3 of all ADRs and are thought to affect 0.2 -3% for the general patient population, and potentially up to 15-20% of hospitalized patients. In veterinary medicine, the incidence of drug allergic reaction has never been investigated. However, drug allergy experts believe it is similar to what is observed in humans when considering veterinary patients such as dogs who often receive similar drugs for similar diseases than their human counterpart.

In human medicine, clinicians’ lack of awareness and knowledge about drug allergy has been shown to affect incidence estimations, but also the prognosis of these reactions.
Thus, the present thesis aim to better understand the impact of drug allergy in veterinary medicine, by characterizing these reactions and their incidence in dogs, and evaluating the awareness amongst veterinarians on the subject.

The survey suggests that there might be a lack of awareness secondary to a lack of teaching specific to drug allergy in veterinary medicine, like has been identified in human medicine previously. Interestingly, For 16.3% of the “likely” and more than half of the “possible” (58.3%) drug allergic reactions identified in our retrospective study, a drug allergy was not mentioned at all in the medical record. Furthermore, only 38.5% of these cases had a drug allergy formerly included in differential diagnosis reported in the patient’s medical record. Both studies therefore reinforce the possibility that lack of awareness could have decreased the incidence of allergic reactions we found in dogs during the retrospective study.

Other data further suggest a lack of awareness or knowledge about drug allergy among veterinarians. Thus, 83.1% of the survey responders indicated only clinical signs matching anaphylaxis (e.g. angioedema, urticaria, respiratory distress) and 1.0% indicated only clinical signs matching delayed reactions (e.g. Erythema Multiforme, Stephen Johnson Syndrome, ITP, IMHA) (figure 6A, table I-IV). Yet, in human medicine, immediate reactions are thought to account for 20-40% of all drug hypersensitivity reactions. In addition, “immediate” reactions represented only 16.7% of all the selected drug allergic reactions. Interestingly, survey participants significantly increased their estimate of drug allergy cases they see per year after reading our short informative paragraph on the subject.

In human medicine the lack of training was identified as a cause of non-recognition of drug allergy cases, leading to poor management and outcome. The impact of an educational initiative on drug allergy was found to have a positive impact and the diagnosis and management
of drug allergy in a tertiary care medical center. Interestingly, data of our survey showed that 43.8% (116) of the responders did not feel confident in recognizing and treating drug allergic reactions. Half of the participants also indicated that the information about drug allergy in the veterinary literature is insufficient. It is possible that the lack of recognition of a possible or likely drug allergy in multiple cases of our retrospective study (eliminated before, or kept for, the final characterization) is also related to an inadequate training about drug allergy during school and/or continuing education for the clinicians involved with these cases. Interestingly, there is no specific requirement from the AVMA for training about drug allergy in the US veterinary school. Amongst the participants, 87.7% indicated being interested in learning more about drug allergy as part of their continuing education (national or regional conferences (63.3%); in-house or university seminars (52.3%); journal articles (62.4%); or online (49%; e.g. webinars or Veterinary Internet Network, VIN)).

In the survey, 79.9% of the responders indicated that their medical record system include a warning system if a patient had a history of suspected or confirmed drug allergic reaction, nevertheless 22.3% of the participants “never” ask and 43.7% “sometimes” ask about previous drug allergy when taking their patient’s history. In addition, 13.4% of participants indicated that they “never” warn and 48.7% “sometimes” warn the owners about drug allergic reaction when prescribing a drug to a patient. Yet, antibiotics, antiparasitics and NSAIDs are the most commonly prescribed drugs in veterinary and they were the most commonly associated with the drug allergic reactions studied in our retrospective study. The risk of drug allergy among dogs is therefore significant.

It is noteworthy that about 40% of the preselected cases during the database searches of our retrospective study had to be eliminated for lack of critical information in the medical record
(e.g. pre-exposure to the culprit drug). Interestingly, such critical information was also missing for certain cases that had been fully followed within our hospital. When suspecting a drug allergic reaction, a thorough review of the patient’s past history (e.g. previous reactions; previous drug exposure; concurrent immune disorder) and details of the reaction itself (e.g. timing, evolution, clinical signs) is critical to the diagnosis. In human medicine, the reporting of drug allergy in the medical record and the quality and completeness of the medical record has been shown to reduce the number of medical errors.31

In conclusion, this thesis identified a lack of awareness towards drug allergy in veterinary medicine, leading to poor recognition of these reaction and therefore poor management. This work also confirmed that drug allergic reactions are potentially as frequent in dogs as they are in human medicine, in addition to sharing very similar clinical patterns. We therefore think that improving education of veterinarians on the subject could have a significant impact: 1) it should improve diagnosis and management of drug allergy cases; 2) it should improve the determination of a more accurate incidence of drug allergy in veterinary patients; 3) #2 should improve funding of research on veterinary drug allergy; #3 should improve #1. In the meanwhile, more research, such as a prospective study, will be needed to better understand the impact of the drug allergic reactions in veterinary medicine, and eventually create guidelines to improve diagnosis and management of these reactions.
REFERENCE LIST


APPENDIX
Dear Colleague,

You can help us advance veterinary medicine.

Our laboratory at UIUC studies drug allergy in both human and veterinary patients. However, to date, very little is known about these reactions in veterinary medicine. The present survey is one of our ongoing projects to improve the lack of knowledge on this subject.

The survey should not take more than 15 minutes and your name will remain confidential in the analysis of any information regarding this study. Survey information will be combined from all participants and be reported in aggregate, only. Your name will not be associated in any presentation or publication of the results.

Thank you in advance for your participation.

Sincerely,

Drs Sidonie Lavergne & Fabrice Fosset

Instructions

This survey is only focused on drug allergy in veterinary medicine.

If you are interrupted during the survey, do not worry, you will be able to take where you left easily. Indeed, SurveyMonkey will have saved your previous answers and will automatically bring you back where you left.

During the survey, you will only be able to navigate forward, so take your time before moving on to the next question. This feature allow a higher quality of the output.

Please focus your answers on your own individual experience rather than your clinic's situation.

You will have the option to skip questions, but please, answer as many questions as possible.

Thanks again for helping us!
1. Did you obtain your DVM degree from the University of Illinois College of Veterinary Medicine?

- Yes
- No
- Yes, but I did not follow my whole DVM training at UIUC before obtaining my diploma.

Thanks for your participation!

If you did not graduate from UIUC, you received this survey by accident. This preliminary study is limited to UIUC graduates. We hope to extend it next year to other DVMs. Hopefully, you will be interested in participating then as well.

For more information on drug allergy in veterinary medicine, here are some references:

Drug hypersensitivity reactions targeting the skin in dogs and cats.
Voie KL, Campbell KL, Lavergne SN

Nephrotic syndrome associated with administration of sulfadimethoxine/ormetoprim in a Doberman.
Vasilopulos RJ, Mackin A, Lavergne SN, Trepanier LA

Have a nice day.

Drs Sidonie Lavergne & Fabrice Fosset

2. When did you graduate from veterinary school?

Year of graduation

If you did not graduate between 1974 and 2014, please specify?

3. Please indicate your year of birth?

Year of birth

---

Page 2
4. Please identify your gender?

- [ ] female
- [ ] male

5. Are you a Board Certified Specialist or in training?

- [ ] Yes
- [ ] No

6. Please specify the specialty.

| Specialty          |  
|--------------------|---|
| Board Certified    |  
| Residency Trained |  
| Intern            |  
| Resident          |  
| Fellow            |  
| Other (please specify) | 

7. Indicate whether you have pursued, or pursuing, a degree in research.

- [ ] PhD
- [ ] Thesis Master
- [ ] Non-Thesis Master
- [ ] None of the above

Other (please specify) 

---
8. Are you presently working in the United States of America?

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</table>

If you working outside of the US, please specify here?

9. Since you received your DVM degree, what professional environment have you been involved with?

Please, indicate the number of years for each applicable environment.

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<tr>
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<td></td>
</tr>
<tr>
<td>Academia/clinic</td>
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<tr>
<td>Industry</td>
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<tr>
<td>Government (e.g. FDA; EPA...)</td>
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</tr>
<tr>
<td>Other (please specify with # of years)</td>
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10. As a clinician, what species do you see, or used to see, the most in consultation?

Please indicate a percentage if more than one category.

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<tr>
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</tr>
<tr>
<td>Dogs and/or cats</td>
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</tr>
<tr>
<td>Exotics/Zoo/Wildlife</td>
<td></td>
</tr>
<tr>
<td>Other (please specify with %)</td>
<td></td>
</tr>
</tbody>
</table>
Drug allergy in veterinary medicine

11. Have you attended a lecture, laboratory, discussion, or school seminar about drug allergy during your DVM training at the UIUC College of Veterinary Medicine?

- Yes
- No
- I do not remember

12. Do you feel that the information regarding drug allergy in your veterinary curriculum is/was sufficient for you to diagnose and treat drug allergic reactions with confidence?

- Yes
- No
- I do not know
- Does not apply (I am not and was never a practicing clinician.)

13. Since graduation, have you attended a presentation about drug allergy?

- No
- Yes

If yes, please specify (e.g. conference seminar; conference lecture; academic seminar series)

14. Since graduation, have you read article(s) about drug allergy?

- Yes
- No
- I don't remember

15. Do you remember the name of journal or the title of the article(s)?
16. Do you feel that the information about drug allergy in the veterinary literature is sufficient?

- Yes
- No
- I do not know

17. Since graduation have you ever worked as a clinician?

- Yes
- No

18. How often do you usually include “drug allergy” or “drug allergic reaction” in your differential diagnosis?
- If you are not practicing anymore, address the question for when you used to be in clinics. -

- Never (none of your patients)
- Sometimes (1-25% of your patients)
- Regularly (26-50% of your patients)
- Often (51-75% of your patients)
- Almost always (76-100% of your patients)
- Always (all of your patients)

19. How many confirmed or highly suspicious cases of drug allergy do you see per year (on average)?
- If you are not practicing anymore, address the question for when you used to be in clinics. -

- None
- 1 to 12
- 13 to 24
- 25 to 60
- > 60
20. When you take the history of a patient, do you or your technician ask specifically whether this patient has any known drug allergy?
- If you are not practicing anymore, address the question for when you used to be in clinics. -

- Never
- Sometimes
- Most of the time
- Always

21. When prescribing a medication to a patient, are you warning the owner(s) specifically about the risk of allergic drug reaction?
- If you are not practicing anymore, address the question for when you used to be in clinics. -

- Never
- Sometimes
- Most of the time
- Always

22. Does your medical record system have a warning system in place when a patient had a previous, suspected or confirmed, drug allergic reaction (e.g. sticker, tag, alert message in the electronic system)?
- If you are not practicing anymore, address the question for when you used to be in clinics. -

- Yes
- No
- I don’t know

23. Please indicate the clinical signs that you might associate with a drug allergic reaction?
24. Please indicate the blood work abnormalities that you might associate with a drug allergic reaction.

25. Select in the list bellow the organ systems that may be targeted during a drug allergic reaction.

- Cardiovascular
- Respiratory
- Nervous
- Skin
- Musculoskeletal
- Blood (including bone marrow)
- Digestive (including liver)
- Endocrine (excluding reproductive organs)
- Urinary (excluding reproductive organs)
- Reproductive
- None of the above
- I am not sure

Other (please specify)

After the following short paragraph on drug allergies, a few more questions...

A drug allergic reaction is an antigen-specific immune reaction that targets a drug or a protein modified by a drug. Such drug allergic reaction requires a prior exposure to the drug (of at least a few days). Once the immune system is sensitized against the drug, the allergic reaction can be immediate (< 24h after drug exposure) or delayed (> a few days or weeks or months of drug exposure). Clinical signs associated with a drug allergic reaction commonly involve the skin, the blood cells, and the liver. However, kidneys, respiratory organs, and other digestive organs can also be affected. Depending on the exact pathological mechanisms, any other organ could be involved (e.g. brain and vasculitis). The diagnosis is usually based on the clinical presentation and the medical history. However, some diagnostic tests, such as tissue biopsies or drug-specific immune tests (e.g. basophil activation test; lymphocyte transformation test) can be conducted.
26. Are you currently working as a clinician?

- Yes
- Not anymore
- I never worked as a clinician.

27. After reading the previous short paragraph on drug allergy, would you change how often you usually include “drug allergy” in your differential diagnosis?
- If you are not practicing anymore, address the question for when you used to be in clinics. -

- Yes
- No
- Maybe

28. After reading the previous short paragraph on drug allergy, would you change how many confirmed or highly suspicious cases of drug allergy do you see per year (on average)?
- If you are not practicing anymore, address the question for when you used to be in clinics. -

- Yes
- No

29. After reading the previous short paragraph on drug allergy, how many confirmed or highly suspicious cases of drug allergy do you see per year (on average)?
- If you are not practicing anymore, address the question for when you used to be in clinics. -

- None
- 1 to 12
- 13 to 24
- 25 to 60
- > 60
30. After reading the previous short paragraph on drug allergy, would you start asking whether your patient has any known drug allergy?

- Yes
- No
- I already do it
- Do not apply to me

31. After reading the previous short paragraph about drug allergy, would you start warning the owner(s) specifically about the risk of drug allergy before prescribing a drug?

- Never
- Sometimes
- Most of the time
- Always
- I already do it
- Do not apply to me

32. Would you be interested in learning more about drug allergy as part of your continuing education?

- Yes
- No, I am not interested in learning more about drug allergy.
- I do not take any continuing education training in general.

33. How you would like to get more information on drug allergy?

- National or regional conference
- Seminars (in house, University…)
- Journal articles
- Webinar
- Other (please specify)
34. Would you consider consulting with a veterinarian specialized in drug allergy for specific cases (past, present or future)?

- Yes
- No
- Not applicable

Suggestions and Comments

35. Feel free to leave any comments or suggestions here.

Thanks for your participation!

For more information or consultation, please email Dr. Sidonie Lavergne (slavergn@illinois.edu).

For more information on drug allergy in veterinary medicine, here are some references:


Thanks again and have a nice day!

Drs Sidonie Lavergne & Fabrice Fosset