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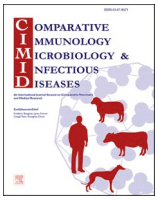

Xanthinuria secondary to allopurinol treatment in dogs with leishmaniosis: Current perspectives of the Iberian veterinary community

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ABSTRACT

Xanthinuria is a significant adverse effect in dogs on long-term allopurinol for treatment of leishmaniosis. The study aims to investigate how the Iberian veterinary community (IVC) identifies, manages, and proactively prevents xanthinuria secondary to allopurinol treatment. A cross-sectional study was conducted using an online survey, translated into two languages, and disseminated to the IVC via social networking forums. Respondents were asked to share their treatment regimens, adverse effects attributed to treatment, as well as preventive and reactive measures against xanthuria. Of two-hundred and thirty respondents, 99.6% prescribe allopurinol for canine leishmaniosis. Xanthinuria was estimated to happen in less than one out of every four dogs by 91.7% of the clinicians. Xanthinuria has been detected by 71.6% of respondents at least once. Three out of every four respondents inform owners about deleterious effects of allopurinol, and 28.4% consider implementing a change in diet in advance of treatment as a proactive measure. To monitor xanthinuria, urinalysis and diagnostic imaging are used by 71.2% and 31% of clinicians respectively. When xanthinuria is detected, 43.2% of the respondents discontinue allopurinol, 24% replace it by nucleotide-analogs, 14.9% reduce its dosage, and 3.1% split its dosage but increase administration frequency. Additional measures are taken by 72.1% of the respondents, 59.4% of whom prescribe a low-purine diet. The IVC recognizes xanthinuria as a fairly common secondary effect of long-term allopurinol treatment in dogs with leishmaniosis and recommends periodically monitoring and preventive measures.

1. Introduction

Canine leishmaniosis (CanLeish) is a global vector-borne, zoonotic disease that is endemic in more than 70 countries, including southern Europe. In particular, CanLeish impacts the Iberian Peninsula due to favorable environmental conditions that support the vector species, sand flies [15].

Leishmaniosis is potentially fatal in affected dogs and clinical recurrences are frequent, therefore medical management is essential to control the disease. Parasitological cures are unlikely; however, available protocols can improve quality of life and life expectancy [9]. In addition, treatment can reduce parasite load and infectivity to sand flies, thereby decreasing the cycle of transmission to other susceptible animals and individuals. Most efficient current treatment protocols include the combination of allopurinol with meglumine antimoniate or miltefosine [24,4,8]. However, allopurinol is considered to be the first line drug for long-term management of CanLeish, because it is widely available, cheap, effective against CanLeish and not used for the treatment of human leishmaniosis [21]. Allopurinol is a purine analog that historically has been used to treat gout in people because, being a xanthine oxidase inhibitor, it reduces serum urate concentration [20]. Its leishmanistatic activity was discovered in the 70s by Pfaller and Marr, and appears to inhibit protein translation within the parasite, causing selective leishmanial death [1].

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Because of its mechanism of action as a xanthine oxidase inhibitor, allopurinol has been associated with adverse urinary effects, specifically renal mineralization and xanthine urolithiasis secondary to xanthinuria. Xanthinuria consists in the urinary excretion of xanthine. Because xanthine is only slightly soluble in urine at any urinary pH, it can lead to and increases the risk of xanthine crystals formation, xanthine shells formation around other uroliths, or even xanthine urolithiasis [17,2,23,24,6]. A 2007 report from the Minnesota Urolith Center disclosed that xanthine represented a mere 0.1% of all uroliths sent to the center, however, almost all had been retrieved from dogs treated with allopurinol (Osborne et al. [13]). Torres et al. [24] reported that xanthinuria was present in 13% of dogs that were being medically managed with allopurinol to treat leishmaniosis, either alone or in combination with other urinary tract conditions, namely renal mineralization (present in 7.5% of dogs) and urolithiasis (present in 6.8% of dogs). The true prevalence of xanthinuria in dogs that receive allopurinol is unknown, but incidence of xanthinuria seems to rise among dogs that are enrolled in long-term therapeutic protocols [2]. This is concerning because xanthine urolithiasis formation is an irreversible process and its dissolution through medical management is not effective [17,24]. Therefore, close monitoring of the urinary tract through urinalysis and diagnostic imaging are an essential tool in all dogs prior to, during, and following allopurinol treatment, providing early detection [12,17,18,23,24]. Even better than early detection could be prevention of urinary consequences secondary to xanthinuria using prophylactic changes in diet, reduction of the urinary specific gravity (USG) by increase water consumption, alkalinization of the urine, and changes in the protocol (dose or frequency) of allopurinol [12,13,17,2,24].

Although these prophylactic measures have been outlined in the veterinary medical literature, it is unknown whether clinicians know about and/or draw upon this knowledge to prevent, diagnose and manage urinary adverse effects associated to allopurinol treatment in CanLeish.

The study aims were: to find out about the commonly used dosing protocols for allopurinol by the Iberian veterinary community (IVC); to assess how the IVC identifies and manages clinical cases of xanthinuria; and to determine which preventative measures (if any) are taken in clinical practice to avoid sequelae, including, but not limited to xanthine urolithiasis.

2. Materials and methods

2.1. Survey development and dissemination

A cross-sectional study was designed to gather information about xanthinuria prevention, diagnosis and management by surveying veterinarians in two languages (Portuguese and Spanish) to solicit responses from the IVC. Prior to dissemination, the survey was reviewed by authors and an epidemiologist and thereafter uploaded to a software platform (Google Forms®) for dissemination to the IVC. The latter was conducted via veterinary restricted online forums on social networking from Portugal and Spain. The survey instrument consisted of a combination of multiple choice, checklist style questions and one free-text response. Depending upon how the respondent answered, completed surveys ranged from four to twenty-six answers. The survey was anonymous. No identifiers were attached to the survey, and respondents were only asked to provide demographic data in the form of age and gender.

The content of the questionnaire was divided into five sections: respondents' age, gender, and country of origin; allopurinol dosing regimens; adverse effects attributed to allopurinol and subsequent withdrawal of the drug; screening tools and diagnosis of xanthinuria; and measures taken to prevent xanthinuria.

Surveys were accessible from 5th November 2020–5 th March 2021 in Portugal and from 15th November 2020–5 th March 2021 in Spain. Participation was voluntary and no incentives for completion were offered.

An English copy of the survey is available as a file in the Supplementary Materials.

To be included in the study, participants were required to certify that they were veterinary professionals, consenting to the anonymous and voluntary nature of the survey.

2.2. Statistical analysis

Data was captured using Google Forms®. Due to the nature of the study and data collected, descriptive statistics was conducted using Microsoft Excel and SPSS (IBM). All results were reported as absolute numbers and percentages. For statistical purposes, responses that involved selecting the "Other option" field were grouped when appropriate.

3. Results

Two-hundred and thirty respondents provided data from two countries: 131/230 (57%) were from Portugal and 99/230 (43%) were from Spain. Most respondents (102/230; 44.4%) were between 26 and 35 years old, followed by 38% (87/230) identified as falling within the 36–45 age group, 12.2% (28/230) were within the 46–55 age group, 3.5% (8/230) were in the 56–65 age group, and 2.2% (5/230) were less than 25 years old.

3.1. Allopurinol prescription regimens

Two-hundred and twenty-nine (99.6%) veterinarians reported that they use allopurinol for medical management of CanLeish. One-hundred and sixty-two (70.7%) veterinarians initiate treatment with a starting dose of 10 mg/kg q12h (70.7%) as compared to 10–20 mg/kg q12h [22/229 (9.6%)], 10 mg/kg q24h [17/229 (7.4%)], < 10 mg/kg q12h [15/229 (6.6%)], 10–20 mg/kg q24h [9/230; (3.9%)], < 10 mg/kg q24h [2/229; (0.9%)], and > 20 mg/kg q24h [2/229; (0.9%)]. None of the respondents reported prescribing a dose more than 20 mg/kg q12h to initiate treatment.

Considering length of therapy, 92/229 (40.2%) of respondents prescribe allopurinol for a duration of 4–6 months as compared to 12 months [64/229 (28%)]. Indefinitely/lifelong [26/229 (11.4%)]; for two or more years [11/229 (4.8%)]; or for an abbreviated course of 1–3 months [4/229 (1.8%)] were also reported. Fourteen percent (32/229) did not clearly specify their recommendations concerning length of therapy.

One-hundred and forty-nine respondents (65.1%) discontinue allopurinol when clinical signs are in remission and serology titers have decreased. Thirty-four respondents (14.9%) discontinue allopurinol at the end of their prescribed protocol (e.g., 6 months) to avoid long-term adverse effects. Fourteen (6.1%) discontinue allopurinol after improvement of clinical signs and/or remission regardless of the duration of therapy, while seven (3.1%) only discontinue the drug after a significant serology titer reduction. Three veterinarians (1.3%) discontinue allopurinol after completing their prescribed protocol because they report no benefit in treatment continuation. Twenty-two veterinarians (9.6%) selected "other option" for this survey question, mentioning other rationales for the discontinuation of allopurinol treatment, such as the development of adverse effects, including xanthinuria.

3.2. Allopurinol withdrawal and adverse effects

One-hundred and twenty-five respondents (54.6%) withdraw allopurinol before its recommended treatment length. Of these, 111/125 (88.8%) cited adverse effects as the primary reason for early discontinuation of therapy. Nine veterinarians (7.2%) cited poor compliance while 2/125 (1.6%) mentioned financial constraints. Three veterinarians (2.4%) selected "other option" and specified their rationale, which

included remission or patient death.

Fifty-seven (24.9%) veterinarians cited adverse effects of allopurinol therapy. From these, 42/57 (73.7%) disclosed an elevation in liver enzymes or associated signs of hepatopathy, 21/57 (36.8%) reported diarrhea, and 17/57 cited nausea (29.8%). Eight (14%) reported cutaneous hypersensitivity/vasculitis while 2 (3.5%) reported non-cutaneous vasculitis (3.5%).

3.3. Xanthinuria detection, estimated frequency, urinary complications, and diagnosis

One-hundred and sixty-four veterinarians (71.6%) have detected xanthinuria in dogs secondary to allopurinol therapy at least once.

When questioned about the estimated frequency of xanthinuria as an adverse effect of allopurinol therapy, 114/229 (49.8%) consider that it occurs in 0–5% of CanLeish cases, 56/229 (24.5%) recognize it in 5–15%, 40/229 (17.5%) in 15–25%, 14/229 (6.1%) in 25–50%, and 5/229 (2.2%) estimate it happening in more than 50% of cases.

In association with xanthinuria, 110/160 (68.8%) of the respondents reported the presence of urinary signs (dysuria, stranguria and pollakiuria), 95/160 (59.4%) reported non-obstructive urolithiasis, 60/160 (36.5%) reported renal mineralization, 50/160 (31.3%) reported bacterial cystitis, 47/160 (29.4%) documented urethral obstruction, 28/160 (17.5%) documented ureteral obstruction, and 7/160 (4.4%) reported "other complications" including, but not limited to, pyelonephritis or nephrolithiasis. (Fig. 1).

One-hundred and twenty-nine respondents (78.7%) have diagnosed xanthinuria by identifying xanthine crystals on urinalysis. Twenty (12.2%) identified xanthine urolithiasis through urolith analysis following surgical removal. Nine (5.5%) assumed xanthine is to be implicated when urolithiasis is observed via abdominal ultrasound. Six respondents (3.7%) described "other" methods of detection, such as a combination of urinalysis and abdominal ultrasonography.

3.4. Xanthinuria prevention, monitoring and reactive measures

One-hundred and seventy-two respondents (75.1%) advise owners about the adverse effects of allopurinol treatment when initiating therapy. Sixty-five respondents (28.4%) consider implementing a low-purine diet at time of allopurinol induction as a prophylactic measure, before xanthinuria has developed.

Routine urinalysis is commonly used to monitor dogs for the development of xanthinuria by 163/229 (71.2%) of respondents. Seventy-one respondents (31.0%) also perform diagnostic imaging as screening tests to assess for urolithiasis and drug-induced renal mineralization.

When xanthinuria develops as a result of allopurinol therapy, 99/229 (43.2%) of respondents immediately discontinue the drug, 55/229 (24%) replace allopurinol with dietary nucleotides and active hexose correlated compounds (AHCC), 34/229 (14.9%) maintain affected dogs on allopurinol but reduce the dose, 12/229 (5.2%) maintain the same drug, drug dosage, and dosing frequency regardless of xanthinuria while 7/229 (3.1%) maintain daily dosage but split it in three times daily (TID), decreasing the given amount of allopurinol per administration (Table 1). Twenty-two respondents (9.6%) selected "other" and described such options as substituting allopurinol for domperidone, combining several measures (e.g., increase the amount of water and wet food), initiating a low-purine diet, or initiating pulsatile therapy (10–20 mg/kg q12h for seven consecutive days each month).

Of the 34 veterinarians who reduce allopurinol dose, 29/34 (85.3%) lower the dose by 50% (85.3%), 4/34 (11.8%) reduce the dose by 25–50%, and 1/34 (2.9%) decrease the dose by 75%.

One-hundred and sixty-five respondents (72.1%) take additional measures to control xanthinuria beyond drug dose adjustments or discontinuation of allopurinol. Ninety-eight (59.4%) recommend instituting a low-purine diet, 25 (15.2%) increase water intake, 25/165 (15.2%) increase the frequency of clinical monitoring while 8/165 (4.9%) encourage wet food consumption. Nine respondents (5.5%) acknowledged additional strategies, including combining the measures described above (Table 2).

One-hundred and forty-eight respondents (64.6%) disclosed that dogs with leishmaniosis experienced no complications secondary to abrupt withdrawal of allopurinol. Forty-one respondents (17.9%) reported that their patients maintained higher or positive serologies for extended periods of time following drug discontinuation. Thirty-one (13.5%) described clinical relapse of CanLeish. Nine (3.9%) had additional details to share, including that they never needed to abruptly discontinue drug therapy or that their patients experienced all of the above.

Table 1
Reactive measures taken by clinicians when facing xanthinuria and allopurinol dosage reduction.

Measures taken when facing xanthinuria	N (229)	%
Stop allopurinol	99	43.23
Replace allopurinol for AHCC	55	24.02
Maintain allopurinol but reduces their dosage	34	14.85
Other	22	9.61
Keep the same therapy	12	5.24
Maintain allopurinol but increases administration frequency	7	3.06

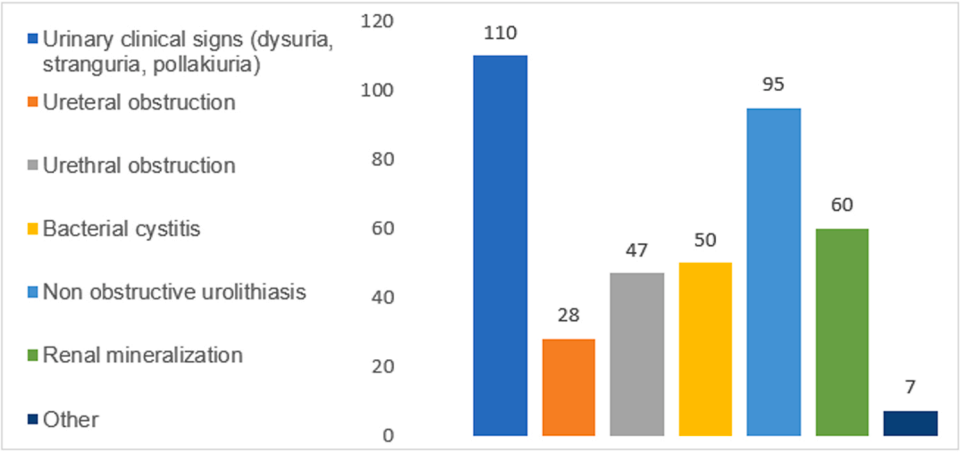

Fig. 1. Complications detected in association with xanthinuria in allopurinol treatments. Note: Respondents could select more than one option, therefore the sum of percentages of different options does not equal 100%.

Table 2
Additional reactive measures taken to control xanthinuria.

Measures taken	N	%
Appropriate dietary change for low-purine diets	98	59.39
Stimulation of water intake	25	15.15
Increase in the frequency of clinical monitoring	25	15.15
Other	9	5.45
Increase in wet food consumption	8	4.85

4. Discussion

As evidenced in this report, the majority (99.6%) of respondents prescribe allopurinol to manage CanLeish. This is in alignment with the current recommendations and guidelines that support its use either as monotherapy or in combination with other compounds, such as meglumine-antimoniate or miltefosine [8,16]. However, although the recommended allopurinol dosage (10 mg/kg q12h) [8] is prescribed by most respondents (70.7%), almost one-third (29.3%) choose to prescribe different dosages. Although the research team did not ask respondents to elaborate on why they prescribed a dose that falls outside of the recommended reference range, the research team speculates that a higher dose was used in some severe cases to ensure an appropriate leishmanistatic activity. However, those that prescribe higher than recommended doses put patients at greater risk for development of xanthinuria and other adverse effects.

Duration of treatment for allopurinol also exhibited great variation. Although most respondents (68.1%) prefer treatment protocols that extend 6–12 months in duration in accordance with the current guidelines [17,24,8], 1.8% of respondents abbreviated treatment while 16.2% prolonged it. This is concerning because higher doses or extended treatment are associated with a higher prevalence of xanthinuria and other adverse effects that are related to the upper and lower urinary tracts [14], while lower dosages or abbreviated treatment protocols may be insufficient to control CanLeish [16].

Prescription of different dosages of allopurinol and variations in treatment length is of concern considering that guidelines of CanLeish management are widely available (Oliva et al., 2010; [22]). Indeed, according to Monteiro [10], 7% of Portuguese veterinarians are not aware of the existence of guidelines for managing CanLeish and even among those who are aware, almost one-third admits not to apply these recommendations in their daily practice. The reasons beyond this could include misinformation, financial constraints, or poor clients' compliance.

The majority of respondents discontinue therapy when remission/improvement in clinical signs associated with a marked decrease in serology are achieved, as previously recommended (Oliva et al., 2010; Solano-Gallego et al. [22]).

When allopurinol was discontinued before its ideal treatment time, it was usually due to adverse effects. Other than xanthinuria, elevated liver enzymes and gastrointestinal signs (diarrhea and nausea) were the most reported complications. These are in line with what has been previously described and may be due to the fact that allopurinol is absorbed in the gastrointestinal tract and requires hepatic metabolization [3,4]. Other adverse effects such as cutaneous hypersensitivity or non-cutaneous vasculitis were also reported. Toxic epidermal necrolysis and drug-induced cutaneous rash with eosinophilia have been reported with allopurinol in dogs [25]. Anyway, these complications are considered very rare.

Almost three-quarters of the respondents have already detected xanthinuria at least once in clinical practice. This high percentage is in agreement with literature, supporting that xanthinuria is the main urinary adverse effect of allopurinol [21,23,24,7]. Primary xanthinuria is rare in dogs [2,24] but its prevalence increases when dogs are treated with allopurinol, particularly those dogs that are being medically managed for CanLeish [24]. About three-quarters of respondents estimated that xanthinuria happens in less than 15% of their cases. Torres et al. [24] described a prevalence of 13% in dogs with leishmaniosis under allopurinol treatment which is actually close to what IVC estimates in daily clinical practice.

Two-thirds of the respondents reported urinary signs besides xanthinuria. Torres et al. [24] reported renal mineralization (57.1%), urolithiasis (50%), and urinary clinical signs (45.2%) in association with xanthinuria. In this study, clinician's perception is overall higher for urinary signs (dysuria, stranguria, pollakiuria) when compared to the remaining urinary findings such as renal mineralization or urethral obstruction. This may be because urinary signs are often noticed at home by owners and can be overrepresented as a chief complain in dogs under allopurinol therapy, when compared to the remaining findings such as renal mineralization, which requires diagnostic imaging to be detected. Therefore, it is questionable if clinical perceptions about urinary signs associated to xanthinuria truly reflects the real percentages of it.

Approximately three-fourths of respondents in this study confirmed xanthinuria via urinalysis. This diagnostic plan is in alignment with current recommendations for monitoring dogs with CanLeish on allopurinol [14,17,23,24]. By contrast, slightly more than 10% of respondents only diagnose xanthinuria upon urolith removal and analysis. This makes it challenging to definitively state that xanthinuria was induced by allopurinol. In these cases, xanthuria could have been pre-existing, albeit unlikely. Furthermore, almost three-fourths of respondents use urinalysis to clinically monitor dogs for the development of xanthinuria secondary to allopurinol while approximately one-third rely upon diagnostic imaging. Urinalysis may be preferred by respondents because it is a cheaper and informative complementary exam, being xanthine crystals easily detectable. This preference aligns with the most recent recommendations stating that urinalysis should be implemented as part of follow-up visits for dogs that receive allopurinol [17,24].

Three-quarters of respondents in this study alert owners about the possible adverse effects of allopurinol; however, less than one-third prescribe a low-purine diet as a preventative measure. The benefit of a low-purine diet is that its consumption reduces the number of purines that are available for the purine synthesis cycle. This in turn reduces the likelihood of xanthinuria [12,2,24]. The fact that only few veterinarians offer this approach may indicate lack of familiarity with the diet or lack of knowledge of its benefits in reducing xanthine crystals and stones formation. Veterinarians may also be less keen to recommend these diets in cases where treatment is already cost-prohibitive. Discussing cost of care is a challenging topic to introduce during clinical consultations.

Diagnostic imaging of the abdomen may involve radiography or ultrasonography. The results of this study demonstrate that abdominal ultrasound is not often performed. This may be due to lack of equipment, lack of user's confidence/competence, or financial constraints. However, abdominal ultrasonography is advantageous because it can detect early renal mineralization that may occur before any evidence of xanthinuria on urinalysis [12,24].

After detecting xanthinuria, most respondents (43.2%) discontinue allopurinol. Some respondents replace allopurinol with other options, including AHCC. Because AHCC is an immune-modulator, it does not induce xanthinuria, and seems to be a good option with similar efficacy to allopurinol in 6 months treatments [19].

Fewer clinicians maintain allopurinol despite xanthinuria but choose to reduce the dosage. The majority reduces it by 50% in accordance with recent recommendations [17]. Even fewer respondents maintain dogs on same allopurinol dose but increase its frequency. Although this strategy is not well documented in literature, the research team infers that this protocol is thought to maintain more constant xanthine excretion throughout the day rather than excretion peaks. Further studies are needed to better support these different approaches.

Almost three-quarters of the respondents acknowledged taking additional measures to control xanthinuria [12,17,2,24]. Among these, switching to a low-purine diet was by far the most common add-on

treatment. Evidence suggests that a low-purine diet minimizes and prevents xanthine urolithiasis. However, to the author's knowledge, no study has been conducted to assess the impact of dietary change on dogs with CanLeish that have allopurinol-induced xanthinuria. Future studies may wish to investigate this further to determine if dietary change is in fact efficacious once xanthinuria has already developed or if it is only beneficial as a preventative measure.

After allopurinol withdrawal, most respondents did not report any complications which highlights that stopping it abruptly is not necessarily associated with worsening or progression of CanLeish. However, clinical relapses have been documented in the veterinary medical literature as well as persistently high serologies. This evidence suggests that discontinuation of therapy can perpetuate the cycle of infectivity and the consequent zoonotic potential of CanLeish [17,18,23]. With the advent of various immunotherapeutic drugs such as AHCC or domperidone, these compounds can be a promising alternative particularly for those cases in which allopurinol withdrawal may be required (Cavalera et al. [19,26]).

This study had several limitations. One of the primary limitations was the small size of its data set. The research team collected responses from 230 respondents; however, this is a fraction of the entire IVC, which has an estimated 40,312 members [5,11]. However, it is unknown which percentage of these members actively works in the field of small animal medicine, the target population for this survey. Regardless of the small fraction, this number of answers is in line with previous survey-studies involving Portugal and/or Spain (Monteiro [27], Oliveira AM, [28], Mattin [29]), supporting that, despite the high number of registered veterinary practitioners, the answer rate is systemically lower than expected. In addition to the small percentage of respondents, most represented the age group of 26–45 years old, meaning that most of respondents are in the beginning of their professional journey as opposed to nearing retirement. This may be a factor of how respondents were recruited, that is, respondents were given access to the survey through social networking. It is likely that social networking captured those who make frequent use of these websites, while inadvertently limiting access to those who prefer alternate methods of information distribution. Finally, another limitation of this study was the question structure and design. For several questions, the research team decided to offer an open-ended alternative in case respondents did not agree with options that were listed for them to choose between. This increased subjectivity in terms of how respondents chose to answer questions, making the statistical analysis more difficult. The research team minimized by grouping the open-ended answers together as one lump sum rather than reviewing each in isolation.

5. Conclusions

This study supports that xanthinuria occurs in dogs on long-term allopurinol to manage leishmaniosis, and that this complication is concerning to many practitioners. However, no clear consensus exists among the IVC about preventing and managing xanthinuria. Further studies are needed to outline clear guidelines on prevention and management of allopurinol-induced xanthinuria in dogs with CanLeish.

Conflict of interest statement

None of the authors has financial or personal relationships that could inappropriately influence or bias the content of the paper.

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Supplementary material

A copy of the survey (translated to English) can be found as a supplementary material to this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.cimid.2022.101783.

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