

# Adverse health consequences associated with canine angiostrongylosis

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Angiostrongylosis, a cardiopulmonary disease caused by infection with the metastrongyloid nematode parasite *Angiostrongylus vasorum*, may lead to serious morbidity, and it continues to be a major health problem for dogs worldwide. This disease spreads to dogs by the ingestion of third-stage larval stage (L3) via the consumption of an intermediate or a paratenic host. The geographic distribution of *A. vasorum* is increasing and the morbidity rate remains high despite progress in anthelmintic treatment and basic supportive care. Angiostrongylosis usually causes dyspnoea, coughing, lethargy, and depression in affected dogs. Dogs may also exhibit a variety of clinical presentations due to multiple organ involvement, which may lead to misdiagnosis and treatment delays. Without appropriate and timely treatment, further health complications can be developed and these may affect the respiratory, vascular, nervous, and/or ocular systems. Therefore, delays in recognition and appropriate treatment of these health complications increase morbidity and mortality rates. This review discusses the main health complications associated with angiostrongylosis, along with appropriate interventions for improving treatment outcomes of these health conditions.

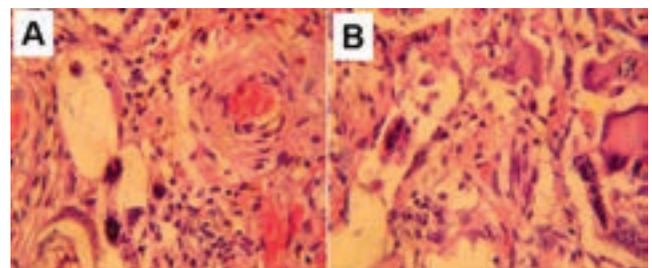
## INTRODUCTION

Canine angiostrongylosis is a parasitic disease caused by the cardiorespiratory metastrongyloid nematode *A. vasorum*. Canines become infected after ingesting the third larval stage (L3), usually within an intermediate gastropod host (slugs/snails) or a paratenic host, such as the common frog (*Rana temporaria*) or chicken (*Gallus gallus domesticus*) (Mozzer and Lima, 2015, Bolt et al, 1993). Infection with this parasite is potentially fatal, and the broad range of clinical signs and high frequency of subclinical infection make detection challenging. The most common clinical signs seen in referral and primary care settings are dyspnoea, coughing, lethargy, and depression, whereas other lungworm-associated signs, such as haemorrhage, are far less prevalent (Koch and Willeßen, 2009; Chapman et al, 2004). The lack of a clear pathognomonic profile and the ambiguity of clinical signs may delay anthelmintic treatment, resulting in more severe pathology. Perhaps the most sinister aspect of angiostrongylosis is that the disease may remain asymptomatic until the dog's health is severely compromised, to the point where the first sign of infection could be the patient's sudden death (Brennan et al, 2004; Bourque et al, 2002). The secondary disease complications caused by *A. vasorum* can include, but are not limited to:

respiratory distress, cardiovascular pathology, hypertension, coagulopathy (with associated haemorrhage), neurological damage and ocular pathology. In the following sections, we describe the adverse health conditions that are associated with canine angiostrongylosis and we discuss appropriate interventions for improving outcomes of each of these conditions.

## RESPIRATORY DISTRESS

Clinical signs relating to the respiratory system are the most common-presenting complaint of infected dogs (Chapman et al, 2004). This is due to the fact that *A. vasorum* eggs hatch within the pulmonary blood vessels to first stage larvae (L1s) and then burrow through the blood vessel wall into the alveoli, causing extensive inflammation (Bolt et al, 1994; Morgan and Shaw, 2010). Granuloma formation throughout the lungs has been documented and these have been found to contain immune cells surrounding a central foreign entity, usually *A. vasorum* eggs or larvae (Bourque et al, 2002). These immune-mediated pathologies can seriously impact on lung function, causing the characteristic cough, dyspnoea and exercise intolerance observed in infected dogs. Interestingly, there has been at least one report of a dog showing no respiratory signs despite obvious lung pathology that was later discovered by radiography (Helm et al, 2009). Radiographically, inflammation can first be visible as an interstitial pattern spreading throughout the lungs, which progresses into a multifocal alveolar pattern, usually to the periphery of the lung fields, after the pre-patent period of five to seven weeks (Chapman et al, 2004; Boag et al, 2004; Koch and Willeßen, 2009). The majority of affected dogs may exhibit alveolar infiltrates and the presence of patchy alveolar pattern in young dogs is a strong indicator for angiostrongylosis (Boag et al, 2004). Besides anthelmintic treatment of the underlying infection, the immunosuppressive activity of corticosteroids



**Figure 1: Lung tissue from an infected dog showing inflammation with macrophages, multinucleate giant cells, and neutrophils. Photo credit: Hany Elsheikha.**

has been advocated in the management of respiratory pathology to reduce inflammation and the fibrosis of lung tissue (Morgan and Shaw, 2010). The use of bronchodilators and provision of oxygen to patients in severe respiratory distress is advisable, but must be tailored to individual cases.

### HYPERTENSION AND CARDIAC ABNORMALITIES

Adult *A. vasorum* reside in the right heart and pulmonary arteries, so understandably, some pathology can be expected here. Koch and Willesen (2009) reported that more than one third of infected dogs reaching referral hospitals display pulmonary hypertension, which is in direct contrast with first-opinion practice where less than 5% of cases developed this condition. This indicates that pulmonary hypertension is more commonly associated with chronically infected dogs or those with a higher worm burden. Pulmonary hypertension was hypothesised to be caused by the inflammatory reaction of the endothelium to worm antigen, causing a thickening of the *tunica intima* and reducing the diameter of the blood vessel (Conboy, 2011). There is the additional effect of the physical presence of larvae or adults on blood flow, as their presence within the pulmonary artery causes a partial occlusion (King et al, 1994; Martin et al, 1993). Syncope is a potential consequence of this and multiple cases have been reported (Conboy, 2011; Chapman et al,

2004; Brennan et al, 2004; Martin et al, 1993). Another relatively frequent finding is cardiac enlargement (usually right-sided) that can be visible via radiography or at post-mortem (Chapman et al, 2004; Brennan et al, 2004; Martin et al, 1993). In severe cases, dogs can develop *cor pulmonale* with right-sided, congestive heart failure and, occasionally, this has resulted in fatality

(Conboy, 2011; Nicolle et al, 2006; Brennan et al, 2004; Bourque et al, 2002). Ascites has been sporadically reported, but does not seem to be a common feature of angiostrongylosis (Novo Matos et al, 2016; Maltman et al, 2013; Nicolle et al, 2006). Both radiography and echocardiography are extremely useful in diagnosing and

assessing the severity of hypertension and cardiac enlargement. The addition of colour Doppler can aid visualisation of blood flow and calculation of arterial pressure (Nicolle et al, 2006). When auscultating a patient with angiostrongylosis, the clinician may discover a heart murmur over the tricuspid valve during systole, as reported by Nicolle et al, 2006. This

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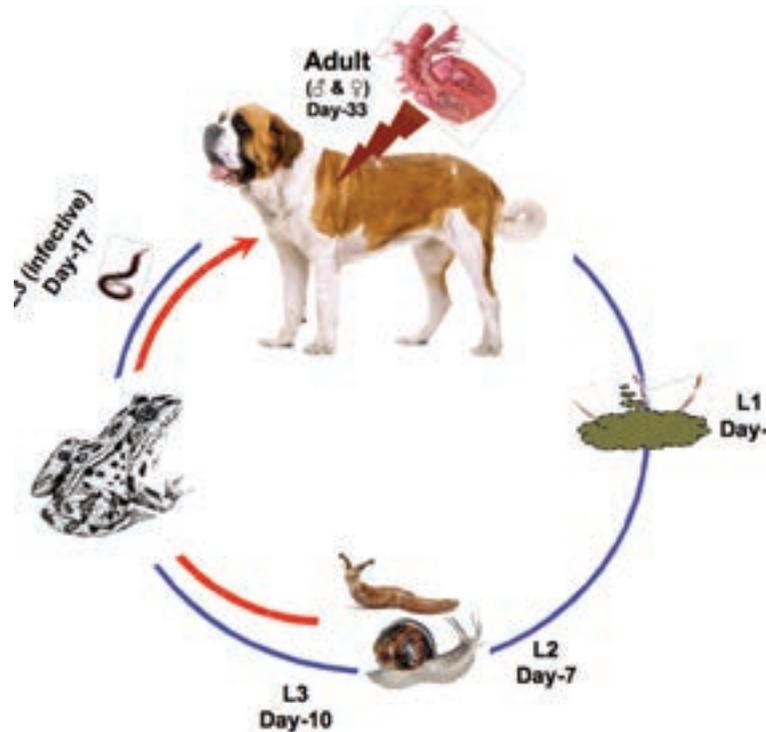
**Figure 2:** An example of ocular angiostrongylosis. Photo credit: Vito Colella, University of Bari, Italy.

finding was later supported when five dogs out of a group of eight naturally-infected dogs had a murmur whose maximum intensity was detected overlying the tricuspid valve (Novo Matos et al, 2016). However, these dogs had to be classified as severely infected before being included in this study, thus the findings may not be apparent in dogs presented at first-opinion practice with a milder infection. Treatment for the clinical signs associated with pulmonary hypertension and cardiac failure includes the use of arteriodilators, angiotensin converting enzyme (ACE) inhibitors and diuretics (Maltman et al, 2013; Nicolle et al, 2006; Brennan et al, 2004). A case of persistent syncopal episodes was successfully treated with the bronchodilator theophylline, however, further research is needed to prove whether this treatment is the most effective (Brennan et al, 2004). The treatment of these clinical signs must take place in conjunction with anthelmintic treatment of the underlying infection. The reversibility of these cardiopulmonary signs has been suggested to be based upon the severity of infection (Koch and Willeßen, 2009).

### COAGULOPATHY

Disseminated intravascular coagulation (DIC) has been well documented as a result of angiostrongylosis and is believed to be caused/triggered by egg deposition in pulmonary capillaries and the damage caused by larval migration. In addition to the inflammatory process, the burrowing of larvae causes multifocal pulmonary damage resulting in an influx of thrombocytes from the circulation to effectively 'plug' the holes created. This causes a systemic thrombocytopenia, reducing the availability of thrombocytes to perform their function elsewhere, hence haemorrhage occurs (Curry et al, 2002). Indeed, a correlation between the reduction in

circulating thrombocytes and patent infection has been reported (Schnyder et al, 2010). The production of immune complexes in response to worm antigen also interferes with the clotting cascade and may exacerbate DIC (Ramsey et al, 1996). Antiplatelet antibodies have been discovered in dogs suffering from angiostrongylosis, indicating that *A vasorum* may cause a secondary immune-mediated thrombocytopenia (Gould and McInnes, 1999; Di Cesare et al, 2015). Despite the lack of a specific haematological/biochemical profile for angiostrongylosis, certain parameters may raise suspicion of angiostrongylosis-induced DIC. These indicators include, besides thrombocytopenia, reduced fibrinogen concentration and an increase in fibrin degradation products, usually combined with an increase in prothrombin time (PT) and activated partial thromboplastin time (APTT; Helm et al, 2009; Ramsey et al, 1996; Maltman et al, 2013; Chapman et al, 2004; Curry et al, 2002). This pattern cannot be attributed to every case and there have been accounts of dogs suffering from thrombocytopenia caused by angiostrongylosis, but with no change in PT or APTT (Gould and McInnes, 1999; Di Cesare et al, 2015). As diagnostic technology advances, it will become easier for clinicians to assess coagulopathy and determine whether it is attributable to angiostrongylosis, with thromboelastography a promising modality (Schnyder et al, 2010). Dogs displaying haemorrhage with elongated PT and APTT (with and without thrombocytopenia) have, on occasion, been misdiagnosed as cases of rodenticide poisoning and treated using vitamin K (Ramsey et al, 1996; Brennan et al, 2004). One of these cases resulted in the death of the patient before the underlying infection was discovered. Whilst this is rare, it is advisable to perform simultaneous faecal and serological testing for *A vasorum* in cases of



**Figure 3: A vasorum lifecycle.**

suspected rodenticide poisoning. Treatment of coagulopathy associated with angiostrongylosis aims to combat the signs of DIC and immune-mediated thrombocytopenia. In cases of acute haemorrhage or when the patient is developing (or is at risk of developing) hypovolemic shock, administration of fresh, frozen plasma or whole blood (preferably type-matched) to replace the missing clotting factors is advised, whilst the underlying infection is treated (Ramsey et al, 1996; Helm et al, 2009; Koch and Willeesen, 2009). The administration of heparin to enhance the action of antithrombin III has been indicated by some clinicians (Maltman et al, 2013; Ramsey et al, 1996). Immunosuppressive therapy before appropriate treatment to remove the underlying infection is not favourable (Maltman et al, 2013). Where the patient isn't displaying signs of life-threatening hypovolaemia, anthelmintic treatment is usually all that is required to remedy the coagulopathy. Koch and Willeesen (2009) found that the clinical signs of coagulopathy were absent one to two days after anthelmintic treatment. Wessmann et al (2006) reported that the PT and APTT of two dogs treated with fenbendazole promptly returned to normal. Likewise, an infected dog's PT and APTT were within the reference range two days after fenbendazole treatment and all parameters were normal at follow-up, 16 days later (Helm et al, 2009). These cases indicate that the coagulopathy associated with angiostrongylosis is reversible if the patient receives timely anthelmintic treatment.

### NEUROLOGICAL DAMAGE

Angiostrongylosis-induced neuropathy develops as a result of either ectopic migration of larvae into the central nervous system (CNS) or haemorrhage into the CNS (Wessmann et

al, 2006). Whilst extremely rare, there have been cases of *A vasorum* larvae or eggs being found within the CNS, either by cerebrospinal fluid (CSF) analysis (Negrin et al, 2008) or by direct visualisation of nematode eggs in brain tissue (Bourque et al, 2002). Neuropathies associated with angiostrongylosis were found to be present in 7% of 124 infected dogs (Morgan et al, 2010). Clinical signs may include depression, ataxia, paresis, paraplegia, and seizures (Denk et al, 2009; Morgan et al, 2010; Di Cesare et al, 2015). Magnetic resonance imaging (MRI) is the modality of choice when assessing neurological damage, with the possible consideration of CSF analysis, however this is contraindicated in patients suffering from increased intracranial pressure due to the risk of brain herniation that may follow the acquisition of the CSF (Denk et al, 2009; Negrin et al, 2008, Wessmann et al, 2006).

In cases of neurological involvement, anthelmintic therapy should be initiated as soon as possible following diagnosis. The supportive treatment offered to the patient depends on the clinical signs displayed. For instance, where the patient exhibits seizures, potassium bromide has proven to be effective in managing this, in conjunction with prednisolone and fenbendazole to treat the underlying infection (Wessmann et al, 2006). The prognosis for patients displaying neurological signs who receive appropriate anthelmintic treatment is generally favourable and reversal of clinical signs is probable (Negrin et al, 2008, Wessmann et al, 2006). The four cases of fatality reported by Denk (2009) and Wessmann (2006) never received anthelmintic therapy which may explain the outcome observed. However, it remains uncertain to definitively claim that these patients would have survived if treated.

**OCULAR PATHOLOGY**

Scleral haemorrhage occurring due to angiostrongylosis was a clinical sign in a significant number of cases (Maltman et al, 2013; Helm et al, 2009; Negrin et al, 2008; Wessmann et al, 2006) whilst sporadic reports of *A vasorum* being found in the eyes of dogs have been described as well (Colella et al, 2016; Manning, 2007; Perry et al, 1991). The migratory route of larvae to ocular tissue remains unknown, but it is believed that the clinical signs that develop are a result of direct tissue damage or *A vasorum* infection-associated haemorrhage (Colella et al, 2016). Diagnosis of ectopic larvae within the eye is possible by direct visualisation using a pen torch. These larvae can be aspirated via anterior chamber paracentesis (ACP) for morphological assessment to determine the species (Manning, 2007). ACP is likely to take place at a referral setting due to the highly specialised nature of the procedure. Thus, faecal examination may be a cheaper alternative for clients, however a negative faecal examination was obtained in a dog that already had *A vasorum* within its eye (Colella et al, 2016). Manning (2007) highlighted the importance of a thorough ocular examination as part of a routine physical examination, in order to identify asymptomatic cases. In a referral setting, treatment of the underlying *A vasorum* infection, along with removal of worms present within the eye via ACP, has shown to be an effective means of treatment (Colella et al, 2016). Although this treatment has proved effective, ACP is a specialised procedure that is scarcely performed even at referral level, so its relevance to cases at primary care level can be limited (Featherstone and Scurrall, 2015). The administration of an appropriate anthelmintic has

the ability to treat ectopic cases of ocular angiostrongylosis (Manning, 2007) and, if treatment is initiated promptly, a complete recovery is possible (Manning, 2007; Colella et al, 2016). Before any conclusions can be drawn regarding prognosis of ocular angiostrongylosis, more in-depth studies are needed including controlled clinical trials.

**CONCLUSION**

*A vasorum* infection continues to spread across many geographic regions, posing a challenge to small animal clinicians due to the heterogeneous and unspecific nature of canine angiostrongylosis. In cases that carry a high suspicion of angiostrongylosis, anthelmintic treatment is advisable even with a negative faecal examination result. Presently, there is not enough evidence to propose the best approach to achieve an optimal management of this disease and its associated health problems. However, satisfactory treatment of canine angiostrongylosis can be accomplished by the use of anthelmintics and supportive treatments, tailored to the associated health complications. Monthly administration of anthelmintic products containing a macrocyclic lactone is the current method of choice for the prevention of *A vasorum* infection. Finally, engagement and education of pet owners, better approaches to clinical surveillance of asymptomatic cases, early recognition of clinical complications, and prophylactic anthelmintic and supportive treatments are the main means for tackling common health complications associated with angiostrongylosis.

**REFERENCES ON REQUEST**

**READER QUESTIONS AND ANSWERS**

**1. INFECTIVE STAGE OF A VASORUM:**

- A First larval stage
- B Second larval stage
- C Third larval stage
- D Egg-containing third larval stage

**2. WHAT ROLE DO SNAILS AND SLUGS PLAY IN THE LIFECYCLE OF A VASORUM:**

- A Intermediate host
- B Paratenic host
- C Definitive host
- D Accidental host

**3. PULMONARY HYPERTENSION IS COMMONLY SEEN DURING:**

- A Acute infection
- B Sub-acute infection
- C Sub-clinical infection
- D Chronic infection

**4. CONTRAINDICATED FOR DOGS WITH BRAIN DISEASE:**

- A MRI imaging
- B CSF analysis
- C CT imaging
- D Faecal examination

**5. A COMMON HAEMATOLOGICAL FINDING IN DOGS WITH ANGIOSTRONGYLOSIS IS:**

- A A reduction in basophils
- B A reduction in eosinophils
- C A reduction in thrombocytes
- D A reduction in neutrophils

**6. FENBENDAZOLE WORKS BY INTERFERING WITH:**

- A B-tubulin and microtubule assembly
- B GABA-gated Cl<sup>-</sup> channels
- C MPTL-1 receptors
- D Acetylcholine receptors

**7. DOGS CAN BECOME INFECTED VIA INGESTION OF:**

- A An infected paratenic host, eg. the common frog
- B An infected slug or snail
- C Free living L3 in the environment
- D All of the above

**8. THE PRE-PATENT PERIOD OF A VASORUM:**

- A 1-2 weeks
- B 3 weeks
- C 5-7 weeks
- D 10-12 weeks

ANSWERS: 1: C; 2: A; 3: D; 4: B; 5: C; 6: A; 7: D; 8: C