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4 Original article

5 Clinical features and long-term follow-up of 70 cases of canine idiopathic eosinophilic lung
6 disease.

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25 The study was carried out at the University of Bristol, University of Edinburgh, University of
26 Liverpool and University of Cambridge.

27 List of abbreviations used in the manuscript.

28 BALF – bronchoalveolar lavage fluid

29 BRON -Cases with bronchial/peribronchial pattern on imaging

30 CT – computed tomography

31 Ct –cycle threshold

32 EB – eosinophilic bronchitis

33 ELD – eosinophilic lung disease

34 EBP – eosinophilic bronchopneumopathy

35 EPG -eosinophilic pulmonary granuloma

36 INT -Cases with interstitial/alveolar patterns on imaging

37 IQR – interquartile range

38 NCI - Cases with no changes on thoracic imaging

39 PCR – polymerase chain reaction

40 Vs – versus

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44

45 **Abstract**

46 Background: Canine idiopathic eosinophilic lung disease (ELD) is sparsely documented in
47 the literature.

48 Methods: Clinical presentation and outcome of dogs diagnosed with ELD(eosinophilic
49 bronchitis or eosinophilic bronchopneumonia) were reviewed. Subgroups were made based on
50 chronicity of clinical signs and findings of thoracic imaging: NCI (no changes in thoracic
51 imaging), BRON (bronchial/peribronchial pattern), INT (Bronchointerstitial/Interstitial/alveolar).

52 Results: Seventy cases were included. There were more young to adult, crossbreed and
53 female dogs. Compared to the other two groups NCI dogs showed lower BALF eosinophilic
54 pleocytosis and absence of circulating eosinophilia, bronchiectasis or death due to respiratory
55 disease.All dogs responded clinically to corticosteroids. Median treatment duration was 4
56 months. Remission (no clinical signs after treatment discontinuation for >1 month) and long-
57 term remission (>6 months) was achieved in 60%, and 51% of patients respectively. Relapse
58 occurred in 26% of cases after remission but was rare (3%) after long- term remission. The 1,2,
59 and 4-year survival to death due to respiratory disease was 98%, 97% and 91% respectively.

60 Conclusion: Prognosis and initial clinical response for ELD was generally good although
61 achievement of long-term remission was only seen in 51% of dogs. Different outcomes based
62 on chronicity of signs, corticosteroid dose, thoracic imaging abnormalities and other clinical
63 variables were not appreciated.

64 Keywords: Eosinophilic bronchopneumopathy; Eosinophilic bronchitis; Asthma; Endoscopy

66 **INTRODUCTION:**

67 Eosinophilic lung disease (ELD) is well-recognized in both human and veterinary
68 medicine and is characterized by eosinophilic infiltration into the airways or the pulmonary
69 parenchyma. Sub-classification has previously been suggested for the dog based on the human
70 classification system and is centred around the affected location (airways vs parenchymal) and
71 the underlying aetiology. [1,2,3,4] ELD has been associated in some instances with parasitic
72 pneumonitis, airway foreign bodies, neoplasia or systemic eosinophilic disease. However, in
73 most instances no underlying aetiology is identified, and the disease is termed idiopathic: i.e.
74 idiopathic eosinophilic bronchitis (EB) or idiopathic eosinophilic bronchopneumopathy (EBP).
75 [1,2,5,6,7,8,9]

76 It is suspected that hypersensitivity plays a role in these cases, but the exact mechanism
77 has not been fully elucidated. [1,5,6,7,8,10] EBP and EB are categorized as separate processes in
78 the human classification [1,3,11], but most of the previous retrospective studies of canine
79 idiopathic ELD have described the disease as EBP and have combined cases with primarily
80 bronchial, peri-bronchial or parenchymal disease into one population. What constitutes EB, as
81 a different entity to EBP, has not been historically well described in canine medicine. [1,2,9, 10,
82 12,13,14] but a recent retrospective study reported the clinical presentation and findings of ELD
83 dogs with a presumptive diagnosis of EB or EBP based on the severity of their bronchoscopy
84 findings [15]. Studies separating canine ELD cases primarily by their thoracic imaging
85 characteristics have not been reported.

86 The two most common idiopathic eosinophilic parenchymal lung diseases in humans are
87 idiopathic acute eosinophilic pneumonia which has an acute presentation, shows more severe

88 alteration in pulmonary function, occurs most commonly in younger male individuals and rarely
89 requires long term treatment; and idiopathic chronic eosinophilic pneumonia characterized by
90 a longer course of presentation, affecting middle-aged to older patients, often female and
91 usually requiring long term therapy. [3,4,11] It is unknown whether similar presentations and
92 associated responses to treatment are observed in canine ELD patients.

93 Previous EBP studies comprised single centres populations and have evaluated the
94 clinical and diagnostic presentation and the short-term response to therapy
95 [2,5,6,9,12,13,14,15,16]. Corticosteroid therapy is the treatment of choice. A favourable short-
96 term response with variable short-term remission and relapse rates has been reported.
97 [1,2,9,12,14] The optimal dose of oral corticosteroids for canine ELD has not been fully
98 elucidated. Inhaled monotherapy with fluticasone has been shown to improve clinical signs in a
99 small single-centre study, however relapses and ongoing clinical signs were observed in the
100 majority of the cases [14].

101 The aims of this paper were 1) to retrospectively describe the clinical presentation,
102 therapeutic management, long-term follow-up and remission and survival rates of a large group
103 of patients diagnosed with ELD in a multicentre population within the United Kingdom (UK); 2)
104 to evaluate the differences in diagnosis and treatment between dogs with acute and chronic
105 ELD, and among dogs with three different appearance on thoracic imaging: no changes,
106 bronchial/peribronchial patten or interstitial/alveolar patterns. 3) to investigate whether the
107 dose of corticosteroids used (anti-inflammatory versus immunosuppressive) had an effect on
108 outcome.

109 **MATERIALS AND METHODS**

110 Ethical approval was obtained from the ethics board of each participating University.
111 Records of all cases with a final diagnosis of EB or EBP diagnosed by a board-certified internist
112 or cardiologist or a supervised resident at four university referral hospitals in the UK
113 (Cambridge, Liverpool, Edinburgh and Bristol) between 2004 and 2016 were reviewed. Follow-
114 up for each case was acquired through the referral centre or via the referring veterinarian's
115 medical records. Cases were only considered if they had a full medical record available for
116 review, presence of clinical signs suggestive of pulmonary disease (coughing, dyspnoea or
117 tachypnoea), thoracic imaging at diagnosis, complete bronchoscopic examination,
118 bronchoscopy-guided bronchoalveolar lavage fluid (BALF) analysis and eosinophilic pleocytosis
119 on BALF results. Eosinophilic pleocytosis was defined as > 10% of the leukocyte differential
120 comprising of eosinophils, with neutrophils accounting for <10%. If neutrophils were >10% the
121 eosinophilic component had to be substantially higher. For cases to be included, parasitic
122 disease had to have been ruled out by one or a combination of: a negative faecal analysis,
123 absence of parasites on BALF analysis or previous regular veterinary approved anti-parasitic
124 therapy. No case had a history of travel outside the UK. Cases were also excluded if any other
125 underlying cause of ELD such as parasitic pneumonitis was identified.

126 The following information was retrieved for each case: signalment, weight, presence of
127 circulating eosinophilia, thoracic imaging findings, bronchoscopy report, BALF cytology results,
128 infectious disease screening results, concurrent diseases, clinical signs and their duration prior
129 to diagnosis, treatment prior to diagnosis or referral.

130 Patients with clinical signs < 1 month were categorized as acute and those with clinical signs > 1
131 month categorized as chronic, similar to the criteria used for human idiopathic eosinophilic
132 pneumonia (11).

133 Thoracic imaging was performed by radiography, computed tomography (CT) or both.
134 All images were reviewed by a board-certified specialist in diagnostic imaging or a resident
135 working under his/her supervision, and sub-classified based on the final report as: no
136 pulmonary abnormalities or pulmonary abnormalities (bronchial/peri-bronchial, interstitial,
137 alveolar) (Figure 1, 2 and 3). CT was used in preference to radiography when both modalities
138 were available. Patients without pulmonary abnormalities were grouped as NCI, and those with
139 pulmonary abnormalities as BRON (if a bronchial/peribronchial pattern was present) or INT (if
140 bronchointerstitial/interstitial/alveolar patterns were present).

141 Bronchoscopy was performed in all patients and reported abnormalities were described
142 as: erythema, oedema, mucus, presence of proliferative changes, bronchiectasis or bronchial
143 collapse (Figure 4,5 and 6). Bronchoscopy findings were subjectively scored based on evaluation
144 of the number of those abnormalities present and graded as: mild (0 - 1 abnormalities),
145 moderate (2-3) or severe (> 4) [2]. BALF was analysed by a board-certified clinical pathologist or
146 a resident under their supervision. BALF results were graded, as previously published [2], based
147 on the degree of eosinophilic pleocytosis: Grade 1-mild- (10-20% eosinophils), grade 2-
148 moderate- (21-50% eosinophils), grade 3-severe-(>50% eosinophils) (Figure 7).

149 Screening for concurrent infectious bacterial respiratory disease was recorded: BALF
150 bacterial culture, *Bordetella bronchiseptica* PCR, *Mycoplasma spp.* PCR or culture.

151 Treatment (dose, duration and route administered) was recorded for each patient. Patients
152 receiving oral corticosteroids were dichotomized based on their dose of prednisolone into anti-
153 inflammatory or immunosuppressive groups: patients needing $\leq 1\text{mg/kg}$ per day or below to
154 control their clinical signs were classified as group A (anti-inflammatory), and patients receiving
155 $> 1\text{mg/kg}$ at some point during the treatment were classified as group I (immunosuppressive).
156 Total response was defined as resolution of clinical signs, partial response as improvement of
157 clinical signs and treatment failure as no improvement of clinical signs. Remission and long-
158 term remission were defined as the full absence of respiratory signs following discontinuation
159 of corticosteroid administration for >1 month and >6 months respectively. Relapse was defined
160 as reoccurrence of clinical signs during remission. Time to remission, length of remission and
161 survival were recorded.

162 **Statistical analysis:**

163 Data were entered into a spreadsheet^a and statistical analyses was performed using two
164 statistical software programs.^{b,c} The level of significance was set at 5% for all analyses. Gaussian
165 distribution was assessed graphically and then with the Shapiro-Wilk test. Baseline descriptive
166 statistics were calculated and reported as percentages for categorical data and median and
167 interquartile range for continuous data.

168 Group comparisons for continuous data were performed with t-test, Mann-Whitney U or
169 Kruskal-Wallis test and chi-square or Fisher's exact test to compare proportions as indicated; no
170 attempt was made to correct for multiple comparisons. Group comparisons were made and are
171 outlined in table 1,2 and 3. When statistical differences were carried out for 3x2 and 3x3 tables
172 further post-hoc analysis was carried out when necessary by looking at the adjusted

173 standardised residuals and carrying out smaller 2x2 direct comparisons to determine specific P
174 values.

175 Time to event analysis was carried out for reaching remission and long-term remission. Kaplan-
176 Meier survival curves were constructed to assess time to remission and time to long term
177 remission between groups and the log rank test was used to compare these. Those not
178 achieving remission, or these lost to follow-up were right censored according their follow-up
179 period. Achievement of remission and the probability of achieving remission and long-term
180 remission was further investigated for other numerous variables (table 3).

181 **RESULTS**

182 **Population**

183 Of the 95 cases initially evaluated, 70 met the inclusion criteria and were enrolled. The
184 25 cases excluded were due to parasitic pneumonitis (2), incomplete investigations (4),
185 complete resolution of signs with anthelmintic treatment (1), and incomplete medical
186 histories (18). Patients comprised of the following breeds: Crossbreed (17), Labrador (7);
187 Springer Spaniel (5); Jack Russel Terrier (5); Cocker Spaniel (4); Siberian Husky (4); Border Collie
188 (2); Border terrier (2); Irish Setter (2); Lakeland terrier (2); Shih Tzu (2); Weimaraner (2);
189 Northern Inuit (2); Parsons Russel terrier (2); followed by one each of the following breeds: Toy
190 poodle, Beagle, Bedlington Terrier, Boxer, Chihuahua, Portuguese Podengo, Maltese,
191 Newfoundland, Golden Retriever, Standard Poodle, Italian Greyhound, Rottweiler. Within the
192 cross-breed group 2/13 (12%) were in the IM-group, 6/17 (35%) within the BRON group and
193 9/17 (53%) within the INT group.

194 Median age was 4 years (IQR 1-6 years). There were 63% (44/70) females, of these 80%
 195 (35/44) were neutered, and 37% (26/70) males, of these 69% (18/26) were neutered. Median
 196 weight was 16.4 kg (IQR 9.4-27 kg).

197 Clinical signs prior to diagnosis were present for a median duration of 2 months (IQR 1-6
 198 months). 48/70 dogs (70%) had clinical signs of > 1-month duration (chronic), and 22/70 dogs
 199 had clinical signs lasting < 1 month (acute) (Table 1).

200 Table 1

	All (n=70)	NCI (n=13)	BRON (n=19)	INT (n=38)	P values ^a	Acute (n=22)	Chronic (n=48)	P values ^b
Age (years)	4 (1-6)	4 (2-6)	4 (2-6)	3 (1-6)	P=0.733	4 (2-6)	2.5 (1-6)	P=0.150
Weight (kg)	16.4 (9.4-27)	15 (9.8-24)	16.5 (9.5-21.5)	16.8 (9.4-29)	P=0.865	14.3 (9.4-28.35)	16.6 (9.8-27)	P=0.810
Circulating eosinophilia	36% (25/70) ^c	0% (0/13)	32% (6/19)	50% (19/38)	P=0.005^{a,d}	59% (13/22)	25% (12/48)	P=0.006^b
Bronchiectasis	14% (10/70)	0% (0/13)	16% (3/19)	18% (7/38)	P=0.255	18% (4/22)	13% (6/48)	P=0.528
Bronchoscopy score (mild, moderate, severe)	37% (25/68), 54% (37/68), 9% (6/68) ^e	46% (6/13), 54% (7/13), 0% (0/13)	32% (6/19), 53% (10/19), 15% (3/19)	36% (13/38), 56% (20/38), 8% (3/38)	P=0.613	38% (8/21), 52% (11/21), 10% (2/21)	36% (17/47), 55% (26/47), 9% (2/47)	P=0.892
Degree of eosinophilia on BALF (mild, moderate, severe)	10% (7/70), 29% (20/70), 61% (43/70) ^f	23% (3/13), 54% (7/13), 23% (3/13)	5% (1/19), 21% (4/19), 74% (14/19)	8% (3/38), 23% (9/38), 69% (26/38)	P=0.021^e	9% (2/22), 27% (6/22), 64% (14/22)	10% (5/48), 29% (14/48), 60% (29/48)	P=0.965
AI	46% (31/67)	62% (8/13)	53% (9/19)	50% (18/38)	P=0.419	50% (11/22)	52% (25/48)	P=0.871
IM	54% (36/67)	23% (3/13)	47% (9/19)	50% (19/38)	P=0.229	50% (11/22)	42% (20/48)	P=0.515
Oral and inhaled steroids	36% (25/67)	38% (5/13)	42% (8/19)	34% (13/38)	P=0.448	32% (7/22)	37.5% (18/48)	P=0.645

201
202 Table 1.

203 A breakdown of the different clinical parameters by the different subgroups can be found.
204 When statistical significance is reached the P value appears in bold. NCI: Cases with no
205 abnormalities on thoracic imaging. BRON: Cases with bronchial pattern on thoracic imaging.
206 INT: Cases with bronchointerstitial/interstitial and/or alveolar pattern on thoracic imaging.
207 Acute: Cases with presenting clinical signs lasting less than 1 month. Chronic: Cases with
208 presenting clinical signs lasting more than 1 month. AI: Anti-inflammatory corticosteroid. IM:
209 Immunosuppressive corticosteroid. BALF: Bronchoalveolar lavage fluid.

210 ^aThere was no difference (P=0.547) in the percentage of dogs receiving previous corticosteroids
211 within the imaging subgroups (NCI 3/10 23%; BRON 3/19 16%; INT 11/38 28%).

212 ^b More dogs in the chronic group (15/48; 31%) received steroids prior to referral than in the
213 acute group (2/22; 9%) P=0.045. If these dogs were excluded from the analysis eosinophilia was
214 still significantly different between both groups (P=0.018) and no difference was observed for
215 any of the other studied variables (All P values higher than 0.150).

216 ^cThere was no difference (P=0.228) in the percentage of dogs with eosinophilia for those dogs
217 who had (4/17; 24%) vs had not (21/53; 39%) received previous corticosteroids.

218 ^dNCI vs BRON **P=0.025**; NCI vs INT **P= 0.001**; NCI vs INT P=0.186

219 ^eThere was no difference (P=0.577) in the severity of bronchoscopy findings severity between
220 dogs receiving (8/17 47%; 8/17 47%; 1/8 6%) or not receiving (17/51 33%; 29/51 57%; 5/51
221 10%) previous corticosteroids.

222 ^fThere was no difference (P=0.951) in eosinophilic pleocytosis in BAL severity between dogs
223 receiving (2/17 12%; 5/17 29%; 10/17 59%) or not receiving (5/53 9%; 15/53 28%; 33/53 62%).
224 previous corticosteroids.

225 ^gNCI vs BRON **P=0.016**; NCI vs INT **P=0.017**; BRON vs INT P=0.890

226 **History and physical examination findings**

227 Clinical signs in patients prior to referral included cough (94%; 66/70), exercise
228 intolerance (17%; (12/70), dyspnoea (16%; 12/70), tachypnoea (14%; 9/70), lethargy (13%;
229 9/72) and nasal/nasopharyngeal signs (10%; 7/70).

230 A minority of patients (7%;5/70), had not received any medical treatment prior to diagnosis,
231 and the remainder (93%; 65/70) had received various combinations of medical treatment
232 including antibiotics (81%; 57/70), non-steroidal anti-inflammatory drugs (33%; 23/70),
233 corticosteroids (24%; 17/70), mucolytic therapy (3%; 2/70) and anthelmintic treatment (76%;
234 53/70) prior to referral.

235 **Diagnostic investigations:**

236 Circulating eosinophilia was reported in 36% (25/70) of patients (Table 1). Faecal
237 analysis was performed in 54% (38/70) patients (Baermann technique (24/38), Zinc floatation
238 (10/38), and direct faecal examination (4/38)). *Isopora spp.* was found in one patient, but not
239 considered to be associated with ELD and this patient was therefore included.

240 All patients had thoracic imaging performed. Thoracic radiographs were obtained from 54%
241 (38/70) patients and thoracic CT from 56% (39/70) patients with both modalities performed in
242 11% (8/70). Diagnostic imaging reports identified a bronchial/peri-bronchial pattern in 27% of
243 patients (19/70), parenchymal (interstitial or alveolar) changes in 54% (38/70) and absence of

244 abnormalities in 19% (13/70). Two patients with an interstitial pattern had also significant
245 parenchymal consolidation on thoracic imaging later confirmed to be canine eosinophilic
246 pulmonary granulomatosis (EPG). Bronchiectasis was identified on thoracic imaging in 14%
247 patients (10/70). The entire study population was subdivided in three groups: no abnormalities
248 on thoracic imaging (NCI), bronchial/peribronchial pattern (BRON) or
249 bronchointerstitial/interstitial/alveolar pattern (INT) (Table 1). CT was used in 77% (10/13)
250 cases in the NCI group, in 37% (7/19) cases in group BRON and in 58% (22/38) in group INT.

251 Full bronchoscopy reports were available for 97% of patients (68/70) with the changes
252 being classified as mild in 38% of cases (25/68), moderate in 54% (37/68) and severe in 9%
253 (6/68) (Table 1).

254 The BALF results were graded as outlined above and were as follows: grade 1 (10%;
255 7/70); grade 2 (29%; 20/70); grade 3 (61%; 43/70) (Table 1). Three dogs had concurrent
256 elevation of neutrophils but in these dogs the neutrophil percentage was <20% and the
257 eosinophilic component >50%.

258 Rhinoscopy was performed in 9% (6/70) of cases and non-infectious chronic rhinitis diagnosed
259 in 5/6 cases. The remaining case had no biopsies taken or diagnosis reached.

260 Bacterial culture of the BALF was performed in 97% patients (68/70). It was negative in
261 79% of cases (54/68) and positive in 21% (14/68). *Mycoplasma spp.* was specifically screened
262 for in 50% patients (35/70) and was isolated in 17% of these patients (4/35). In each case when
263 bacterial infection was identified, clinical records indicated the positive culture was considered
264 to be due to contamination or concurrent infection. This was considered because of a scant

265 (semiquantitatively) growth of an organism and/or no initial response to antibiotics, and a good
266 subsequent response to steroid therapy in the context of a BALF eosinophilic pleocytosis.

267 **Treatment**

268 In some patients, there was an initial treatment trial with fenbendazole (74%; 52/70) or
269 antibiotics (53%; 37/70) prior to the administration of corticosteroids. No patient had
270 resolution of clinical signs with these treatments alone. Corticosteroids were administered to
271 all patients either at the time of diagnosis or when they failed to respond to antibiotic and, or
272 anthelmintic therapy. The breakdown of corticosteroid therapy by dose and route is outlined
273 in Figure 8.

274 Of the patients initially receiving only oral anti-inflammatory corticosteroids, 5.6% (2/36)
275 subsequently required an increase to an immunosuppressive dose to control their clinical signs.

276 Overall, 24% (6/25) of patients receiving dual therapy had their oral corticosteroid therapy
277 discontinued and were managed solely with inhaled corticosteroid monotherapy (Table 1).

278 Overall treatment duration range was 1-103 months (median 4 months, IQR = 2-17 months).

279 **Follow-up**

280 Duration of follow-up for each case was defined as the time from referral until: the
281 present day/they were lost to follow-up/their death. Follow-up ranged from 1 - 140 months
282 (median 29months, IQR = 11-50 months). During follow-up, 7% (10/70) of patients were
283 euthanized or died. Of these 2/10 were due to progression of their respiratory disease (one
284 patient 3 months' and 38 months' post-diagnosis). The remainder died or were euthanized due
285 to non-respiratory related illnesses.

286 The 1,2, and 4-year survival to death due to respiratory disease was 98%, 97% and 91%
 287 respectively (Table 2).

288 Table 2

	All (n=70)	NCI (n=13)	BRON (n=19)	INT (n=38)	P values	Acute (n=22)	Chronic (n=48)	P values
Total response (Absence of clinical signs)	93% (65/70)	85% (11/13)	95% (18/19)	95% (2/38)	P=0.442	95% (21/22)	92% (44/48)	P=0.568
Partial response (Improvement of clinical signs)	7% (5/70)	15% (2/13)	5% (1/19)	5% (2/36)	P=0.442	5% (1/22)	8% (4/48)	P=0.568
Remission	60% (42/70)	61% (8/13)	63.2% (12/19)	58% (22/38)	P=0.922	63% (14/22)	58% (28/48)	P=0.674
Long term remission (>6 months)	51% (28/55)	36.4% (4/11)	58% (7/12)	53% (17/32)	P=0.533	56% (10/18)	35% (14/40)	P=0.141
1,2,4 year survival to respiratory disease	98%, 97%, 91%	100%, 100%, 100%	92%, 89%, 88%	97%, 96%, 92%	N/A	94%, 92%, 88%	100%, 100%, 93%	N/A

289

290 Table 2.

291 A break-down of the different therapeutic response by different subgroups can be found. When
 292 statistical significance is reached the P value appears in bold. NCI: Cases with no abnormalities
 293 on thoracic imaging. BRON: Cases with bronchial/peribronchial pattern on thoracic imaging.
 294 INT: Cases with interstitial/alveolar pattern on thoracic imaging. Acute: Cases with presenting

295 clinical signs lasting less than 1 month. Chronic: Cases with presenting clinical signs lasting more
 296 than 1 month. N/A: Non-applicable. The n= represents the total number of cases. For some
 297 variables the number may be less than the total patient population if the full information about
 298 that case for that variable was not available.

299

300

301 All patients showed a positive clinical response to corticosteroid therapy. Total response
 302 was observed in 93% (65/70) of cases and a partial response in 7% (5/70) of cases. Remission
 303 was achieved in 60% (42/70) of cases and long-term remission in 51% (28/55) of cases.
 304 Treatment duration was 3 months (IQR 2-5 months) and 28.5 months (IQR 16-40 months) for
 305 those achieving and not achieving remission respectively. Treatment duration for those
 306 achieving long term remission was 3 months (IQR 2-5months). Relapse was reported in 26%
 307 (11/42) of cases, 24% (10/42) in the first six-months following discontinuation of corticosteroid
 308 treatment and in 3% (1/28) at least six-months after stopping corticosteroid therapy. (Table 2).
 309 Group comparisons and the non-parametric log rank test showed that the median time to
 310 remission was not different between any sub-groups (table 3).

311 Table 3

	Remission	P Value	Long term Remission	P Value
Anthelmintic prior to ref. (Yes/No)	63% (35/55) / 47% (7/15)	P=0.234	54% (25/46) / 33% (3/9)	P=0.249
Bronchiectasis (Yes/No)	40% (4/10) / 63% (38/60)	P=0.163	40% (2/5) / 52% (26/50)	P=0.609
Eosinophilia (Yes/No)	64% (16/25) / 57% (26/45)	P=0.611	71% (12/17) / 42% (16/38)	P=0.051
Bronchoscopy score (mild/moderate/severe)	64% (16/25) / 60% (22/37) / 50% (3/6)	P=0.811	57% (12/21) / 51% (15/29) / 0% (0/3)	P=0.179

Eosinophilic grade BALF (mild/moderate/severe)	70% (5/7) / 55% (11/20) / 61% (26/43)	P=0.743	66% (4/6) / 44% (7/16) / 51.5% (17/33)	P=0.628
Corticosteroid dose (AI/IM)	56% (20/36) / 64% (20/31)	P=0.456	41% (11/27) / 61% (10/26)	P=0.130
Corticosteroid dose (AI-IN /AI+IN /IM)	62% (13/21) / 48% (7/15) / 63% (20/31)	P=0.496	50% (7/14) / 31 % (4/13) / 62% (16/26)	P=0.193

312

313 Table 3.

314 Comparison by subgroups of achievement of remission (total response in > 1month) and long-
315 term remission (>6m of remission).

316 When statistical significance is reached the P value appears in bold. In dichotomous variables
317 the percentages of remission and long-term remission achieved by both categories can be seen.
318 For variables with three categories percentages of the three categories achieving remission or
319 long-term remission are depicted.

320 BALF: Bronchoalveolar lavage fluid. AI: Anti-inflammatory corticosteroid (all group) IM:
321 immunosuppressive corticosteroid. AI-INH: Anti-inflammatory corticosteroid without inhaled
322 therapy. AI+INH: Anti-inflammatory corticosteroid with inhaled therapy.

323

324 **DISCUSSION**

325 To the best of the authors' knowledge this is the first and largest multi-centre study of
326 idiopathic canine eosinophilic lung disease evaluating clinical features and long-term outcome.
327 We identified a similar age of onset (most young adult) and sex predisposition (more females)
328 in our study population to those reported in most previous publications [1,2,9,12,13,14]. Similar
329 to a recent publication [15] crossbreed dogs were the most common breed reported. This was
330 different to all previous studies in which crossbreeds were reported only very sporadically

331 [1,2,9,12,13,14]. The most commonly reported breeds in those studies included Siberian
332 Huskies [1,2], Labradors [9] and Cocker Spaniels [12], all of which were similarly highly
333 represented in our study. The high proportion of crossbred dogs cannot be explained by the
334 differences in inclusion criteria, as they were present across all imaging subgroups and all dogs
335 in group INT (and also dogs in group BRON in some studies) would have met criteria for
336 inclusion in previous EBP studies. It is possible that the increased representation of crossbreeds
337 may reflect the hospital or regional population characteristics or the increasing awareness of
338 the disease over the past years.

339 Previously it has been hypothesised that younger dogs with EBP may be more difficult to
340 manage [1,17]. This was not observed in our study where a similar treatment response and
341 remission rate was observed for younger and older dogs.

342 Cases were also dichotomised into acute and chronic presentation, similar to the human
343 classification [3,4,11]. In contrast to the situation in human medicine, other than acute cases
344 having a higher incidence of circulating eosinophilia, no other significant differences were
345 found with regards to age of presentation, severity of clinical findings or outcome. Therefore,
346 we did not conclude that separating these two groups provided pertinent clinical information
347 for the management and prognosis of ELD in dogs.

348 Whether different ELD entities with pathophysiological, clinical, therapeutic and/or
349 prognostic differences occur in dogs is currently unknown. In humans, different disease entities
350 with different management and outcome such as pneumonias (acute and chronic), eosinophilic
351 bronchitis, eosinophilic bronchiolitis and asthma are described [11]. In human medicine
352 idiopathic eosinophilic pneumonia is typically associated with pulmonary abnormalities on

353 thoracic imaging and eosinophilic bronchitis is characterized by the absence of pulmonary
354 abnormalities on thoracic imaging. [3,4,11] By dividing our population into three groups in
355 regard to their imaging findings we were able to identify a population of dogs (NCI) with
356 isolated airway disease which would represent EB. At the other side of the spectrum dogs the
357 INT group would be truly airway-parenchymal disease (EBP) and several differences were
358 observed between these two groups of dogs. NCI dogs had less severe eosinophilic pleocytosis
359 on BALF, absence of circulating eosinophilia and absence of bronchiectasis. Additionally, no
360 dogs in this group succumbed to their respiratory disease. Considering the age and time of
361 presentation was similar to the INT cases, it is unlikely that dogs in the NCI group represent an
362 early stage of the disease process and this group likely constitutes true isolated airway disease.
363 Whether the dogs in the BRON group had EB or EBP or whether they constitute a different
364 entity is unknown. In our study they showed similar clinical and laboratory characteristics to the
365 INT group and showed similar differences compared with the NCI group. As the BRON group
366 was the one where CT was used less frequently (37%) it is possible that at least some of these
367 dogs would have shown interstitial changes on CT and indeed belonged to the INT group. A
368 recent paper [15] also attempted to separate ELD into EB and EBP. In this paper however, the
369 definitive criteria to separate both processes were the severity of bronchoscopy findings and
370 dogs could be classified as EB or EBP with a bronchial radiographic pattern: EB had milder
371 bronchoscopic findings and EBP more severe ones. After classification, EB cases in that study
372 ended being mostly cases with absence of radiographic findings, similar to our NCI group, and,
373 similar clinical differences to the findings in our study were observed in regard to blood and
374 BALF eosinophilia and bronchiectasis when compared to the group classified as EBP. No other

375 paper has attempted to separate bronchial vs parenchymal disease in canine ELD. Previous EBP
376 papers vary in inclusion criteria and in some of them the EBP group would have encompassed
377 just the INT group while in others both the INT and the BRON group would have been
378 considered EBP [1,2,9,12,13,14,18,19]. Overall however, in our study, outcomes for all
379 subgroups were not significantly different: response and remission rates were similar with the
380 only exception that, as mentioned previously, death or euthanasia due to respiratory disease
381 did not occur in the NCI group. However, as death was such a rare event in our study it is
382 difficult to make conclusions in this regard.

383 A population which may represent a different ELD disease entity are dogs with EPG. In
384 our patient population only two dogs, both in the INT group, were diagnosed with EPG making
385 it challenging to draw meaningful conclusions. Historically however, dogs with EPG have been
386 suspected to represent a more severe form of ELD with a worse prognosis [19,20,21,22].
387 Consistent with this perception one of the two patients in our population who succumbed to
388 their respiratory disease had a diagnosis of EPG. A recent study [15] suggested a more
389 favourable prognosis for dogs with EPG dogs. However, the diagnosis of EPG dogs in this study
390 was based on a different diagnostic criteria to the usual historical EPG definition of
391 parenchymal lung disease and pulmonary granulomas (consolidation or masses) characterised,
392 when histopathology is performed, by a large population of eosinophils usually with
393 macrophages and epithelioid cells [19,20,21,22]. In this recent study [15], dogs were classified
394 as EPG if they had, on bronchoscopy, airway disease with intraluminal eosinophilic mass lesions
395 (plugging), irrespectively of the presence or absence of parenchymal involvement on thoracic
396 imaging.

397 Circulating eosinophilia, bronchoscopic findings and the degree of eosinophilic
398 pleocytosis was similar in our study to previous EBP studies. The incidence of bronchiectasis in
399 our population was slightly lower compared to the 26-60% reported in previous studies
400 [2,11,13] and a slightly lower incidence of bronchiectasis persisted when only the INT group
401 was evaluated. Bronchiectasis was not identified in any patient assigned to the NCI group.

402 Historically the treatment of choice for EBP has been corticosteroids, and as was
403 observed in this study, good initial responses have been reported [1,2,5,9,12,14].
404 Immunosuppressive therapy has been advocated for the treatment of EBP in the dog [1,2]
405 however, up to 40% of dogs in this study had control of their clinical signs with corticosteroids
406 administered at an anti-inflammatory dose (although 42% of these patients also received
407 concurrent inhaled corticosteroids therapy). Of those patients starting treatment with anti-
408 inflammatory corticosteroids, 5% required an increase dose to immunosuppressive
409 corticosteroids to achieve control of their clinical signs. There was no statistical significance
410 when comparing corticosteroid doses between the different subgroups which would suggest
411 the choice of anti-inflammatory or immunosuppressive dose reflected individual clinician
412 preference and not the type or severity of the ELD.

413 The overall remission (60%) and long-term remission (51%) rates were modest and
414 similar among the different subgroups; and they were also similar to the remission rates
415 reported in previous EBP publications (30-50%) [2,10]. The relapse rate in our study (26%) was
416 also similar to previous reports (30-72%). Importantly, in our study, it was noted that if relapse
417 occurred, it was most likely to occur during the first 6 months following discontinuation of
418 corticosteroid therapy. Once long-term remission was achieved relapses were very rare.

419 Similar to previous EBP studies, death or euthanasia due to respiratory disease was a
420 rare event in our population and 1, 2 and 4-year survival to respiratory death exceeded 90%. As
421 death was such a rare event, no comparisons can be made among groups, however as
422 mentioned above none of the NCI population died or were euthanized due to respiratory
423 disease and one of the two patients that died due to respiratory disease had a diagnosis of EPG.

424 No obvious association was observed between any of the other studied variables
425 indicative of clinical severity (bronchiectasis, eosinophilia, bronchoscopy score, eosinophilic
426 grade) and any of the outcome variables. There was also no difference between dogs receiving
427 anti-inflammatory vs immunosuppressive doses of corticosteroids with regard to likelihood of
428 remission or long-term remission. These results were also similar if the anti-inflammatory group
429 was broken down into those with or without concurrent inhaled therapy. Therefore, a high
430 proportion of dogs appear to achieve remission and long-term remission without using higher
431 immunosuppressive dose which may be associated with increase risk of side effects. However,
432 this is a retrospective paper with several limitations and further specifically designed
433 prospective studies are needed to determine the optimal corticosteroid dose in the
434 management of ELD. It would be of particular interest to investigate whether the remission
435 outcomes observed in this and previous papers could be improved and whether different
436 strategies should be instigated for EB dogs compared to EBP dogs.

437 There are several limitations of this study. Firstly, it has the intrinsic limitations of a
438 retrospective multi-centre study performed over a 12-year period, including non-standardised
439 treatments and recording of clinical records and a referral population bias. We attempted to
440 minimize this by directly contacting the owner and the referring veterinary surgeon when

441 needed and by collecting a large amount of data, which could counteract some of the errors.
442 Secondly, as in every previous EBP study, response and remission is usually assessed by the
443 owner's perception of resolution of clinical signs and not by the objective documentation of
444 absence of intrapulmonary disease. Treatments were not standardised, and the dose, length
445 and protocols used varied among the different clinicians managing the cases. In our institutions
446 anti-inflammatory doses of prednisolone are usually 0.5 to 1 mg/kg per day and
447 immunosuppressive doses are always above 1.5-2mg/kg but scientific evidence and consensus
448 of what dose causes immunosuppression is lacking [23]. Also, the use of mg/m² rather than
449 mg/kg for larger breed dogs has been anecdotally suggested. Unfortunately, we could not
450 retrieve the fluticasone dose accurately from the notes in all cases but in our institutions
451 fluticasone is usually started at 125ug or 250 ug twice a day for dogs <10kg or >10kg
452 respectively and the advice is to administer the dose after placing the mask. Thirdly we carried
453 out many statistical tests, which can lead to type I error, and a higher number of cases would
454 have been preferable to avoid type II error. We elected not to mathematically correct the result
455 to prevent type I error but to report all of them and analyse them critically. In this manner most
456 significant results reported appear robust in our opinion, although caution may be elicited with
457 the higher P values (e.g. between 0.05 and 0.010) observed. Similarly, when subgroups were
458 compared, all the negative results showed, for the most part, very similar populations and
459 although statistical differences might be found with a larger study population we suspect that
460 for the majority of comparisons it is unlikely that these would be of clinical significance.
461 Lastly, despite utilising strict inclusion criteria, inherent limitations remained. Firstly, a
462 consensus of what constitutes eosinophilic pleocytosis in BALF of normal dogs is not clearly

463 defined in the current literature [1,2,10,13, 24,25]. Similar to previous EBP studies
464 [2,7,10,13,14,16,19] we elected to consider eosinophilia >10% in BALF abnormal, however
465 some previous studies have used a marginally higher cut off [7,10,13,14]. Secondly, chronic
466 bacterial respiratory tract infection has been associated with a mixed cell infiltrate on BALF and
467 theoretically could result in higher percentage of eosinophils in BALF [1]. There were however
468 only three included cases with mixed pleocytosis and these cases all had a low proportion of
469 neutrophils (<20%) and high proportion of eosinophils (>50%), thereby meeting the previously
470 suggested diagnostic criteria for ELD in dogs with mixed pleocytosis [26]. Thirdly, parasitic
471 pneumonitis is an important differential for ELD and the ruling out of this aetiology is an
472 essential, yet challenging aspect to the diagnosis. We elected to use the same criteria as in
473 previous studies [1,5,6,9, 13,14] however, absolute certainty in ruling out parasitic disease
474 cannot unfortunately be achieved. Despite this caveat, no statistically significant difference
475 was found between patients that had received adequate anti-parasitic therapy and patients
476 that had not received such treatment. Fourthly, a percentage of dogs received corticosteroids
477 prior to presentation, and this may in theory alter several findings such as the degree of
478 eosinophilia, the bronchoscopy score or the degree of eosinophilic pleocytosis in BAL.
479 However, although we were not able to confirm this in all cases from the notes, it is routine
480 policy in all the hospitals involved in the study to try to stop medications at least one week
481 before seeing the cases. Also, there was no differences in the overall percentages of
482 eosinophilia, bronchoscopy score or degree of eosinophilic pleocytosis when dogs with previous
483 corticosteroids were compared to those without them. The percentage of dogs in which
484 corticosteroids was used prior to the initial appointment was also similar among dogs in the

485 different imaging groups and although it was significantly higher in the chronic group than in
486 the acute group when cases with previous glucocorticoids were excluded from analysis the
487 overall results for the three studied variables were very similar. For all these reasons we do not
488 believe that previous use of glucocorticoids is likely to have had a significant impact of the study
489 results.

490 Lastly, there was a proportion of dogs where imaging classification was carried out by
491 radiography rather than CT and this may have led to group misclassification. This was likely less
492 relevant for the NCI group as nearly 80% of them had CT performed and specific characteristics
493 could be observed for this group however, as mentioned above, only 37% in group BRON were
494 diagnosed by CT and we cannot ruled out that some of these cases would have been classified
495 as group INT if CT had been performed.

496 In conclusion, we report the clinical presentation, therapeutic management and long-
497 term outcome of a large cohort of dogs with ELD in the UK. Dogs in this population were
498 predominantly young, female and crossbreed. The study also showed that dogs without
499 imaging changes, which likely represent EB, have less severe eosinophilic pleocytosis on BALF or
500 circulating eosinophilia than dogs with parenchymal changes suggestive of EBP. Moreover, no
501 dog within this subgroup had bronchiectasis or died due to respiratory disease. However, a
502 noticeable difference however in response to treatment among the different imaging
503 subclassifications or between acute and chronic presentations was not identified. A complete
504 response was achieved in the vast majority of dogs with ELD with the use of corticosteroid
505 therapy, and we found modest remission rates and long-term remission rates of 60% and 51%
506 respectively. Relapses typically occurred during the first 6 months of remission but were rare

507 after long-term remission. In many patients, total response, remission and long-term remission
508 is achieved with anti-inflammatory doses of corticosteroids, however a small percentage of
509 dogs required dose increases to an immunosuppressive corticosteroid dose. Other factors, such
510 as severity of the clinical findings or age of presentation, were also investigated in this study but
511 found not to be significantly associated with outcome.

512 Conflicts of interest statement:

513 No conflicts of interest to declare.

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522

523 Footnote

524 a- Microsoft Office Excel 2007

525 b- R version 3.0.2, R Core Team (2013). R: A language and environment for statistical

526 computing. R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org/>

527 [c-SPSS 23, IBM](#)

528

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594 Leyends

595

596 Figure 1.

597 Radiography of a dog with eosinophilic lung disease showing bronchial pattern.

598

599 Figure 2.

600 Radiography of a dog with eosinophilic lung disease showing bronchointerstitial pattern.

601

602 Figure 3.

603 CT scan of a dog eosinophilic lung disease showing bronchial thickening, peribronchial

604 infiltrations and a multifocal widespread ground glass (interstitial) pattern.

605

606 Figure 4.

607 Endoscopic image of a dog with eosinophilic lung disease showing severe mucosal erythema

608 and inflammation and mild presence of mucus.

609

610 Figure 5.

611 Endoscopic image of a dog with eosinophilic lung disease showing a large amount of thickened

612 mucus.

613

614 Figure 6.

615 Endoscopic image of a dog with eosinophilic lung disease with evidence of severe

616 bronchiectasis.

617

618 Figure 7.

619 Bronchoalveolar lavage cytology of a dog with severe eosinophilic pleocytosis.

620

621 Figure 8.

622 A breakdown of the corticosteroid treatment administered to the studied eosinophilic lung

623 disease population of the current study. Immunosuppressive therapy was considered when a

624 dose equal or more than 1mg/kg per day of prednisolone was administered. Fluticasone was

625 used in all dogs as inhaled therapy.

626