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The full details of the published version of the article are as follows:

TITLE: Retrospective evaluation of the clinical presentation, magnetic resonance imaging findings, and outcome of dogs diagnosed with intracranial empyema (2008–2015): 9 cases

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JOURNAL: Journal of Veterinary Emergency and Critical Care

PUBLISHER: Wiley

PUBLICATION DATE: 20 June 2019

DOI: <https://doi.org/10.1111/vec.12859>

1 **Abstract**  
2

3 **Objective** – To describe the clinical presentation, advanced imaging findings, and short and  
4 long term outcomes in dogs with intracranial empyema.

5 **Design** – Retrospective case series

6 **Animals** – Client owned dogs diagnosed with intracranial empyema

7 **Methods** – Medical records from 2 referral hospitals were searched for dogs diagnosed with  
8 intracranial empyema. To be included in this study, dogs had to fulfill 1 or more of the  
9 following 3 inclusion criteria: a magnetic resonance imaging (MRI) scan with space occupying  
10 accumulation of extra-axial material suggestive of empyema, a cerebrospinal fluid analysis  
11 suggestive of empyema, or direct visualization of purulent material during intracranial surgery.

12 **Results** – Nine dogs with intracranial empyema were included, with a median age of 3.5 years  
13 (range 4 months-12.5 years). All presented as emergencies with 7 of the 9 dogs showing  
14 neurological abnormalities and 2 of the 9 with retro-bulbar swelling and exophthalmos. Six  
15 had surgical intervention, one was medically managed and the remaining two dogs were  
16 euthanized. Typical MRI findings included extra-axial, T1-weighted hypo to isointense, T2-  
17 weighted hyperintense material compared to grey matter with varying degrees of contrast  
18 enhancement, with 6/8 showing evidence of contiguous infection from adjacent structures on  
19 MRI. Seven had one or more samples sent for culture and sensitivity with *Enterococcus*  
20 (surgical swab), *Streptococcus pneumonia* (from CSF) and coagulase positive *Staphylococcus*  
21 (ear swab) being cultured. The median antimicrobial course length was 6 weeks (range 2 – 28  
22 weeks). All dogs for which treatment was attempted survived to discharge, with a median  
23 hospitalization time of 7 days (range 4-10 days). Four of the seven are still alive at the time of  
24 writing (1 lost to follow up; 2 euthanized for other reasons) with all four considered  
25 neurologically normal with a successful long term outcome.

- 26 **Conclusions** – Although intracranial empyema in dogs is a rare condition, excellent outcomes  
27 are possible in those cases treated appropriately.

## 28 Introduction

29

30 Intracranial empyema is a neurological emergency that once diagnosed, requires rapid  
31 and aggressive intervention that comprises both surgical and medical management.  
32 Mechanisms of infection are thought to include hematogenous spread from other foci within  
33 the body (e.g septic emboli), contiguous infection from adjacent structures (inner ears,  
34 cribriform plate, sinuses and eyes), direct access (trauma, bite wound, iatrogenic  
35 (surgery/cerebrospinal fluid (CSF) acquisition)) and migration of foreign bodies or aberrant  
36 parasites<sup>1-5</sup>. Infectious agents reported to be implicated in intracranial empyema include  
37 *Staphylococcus* spp., *Streptococcus* spp., *Nocardia* spp., *Pasteurella* spp., *Actinomyces* spp.,  
38 *Fusobacterium* spp., *Bacteroides* spp. And *Peptostreptococcus* spp and occasionally fungal  
39 organisms<sup>5-7</sup>.

40 Intracranial empyema is a relatively rare condition, which is reflected in the limited  
41 number of reports currently in the veterinary literature, particularly concerning dogs. Although  
42 uncommon in people, intracranial empyema has been extensively described in the human  
43 medical literature with decompressive surgery and culture considered to be the gold standard  
44 in management of human cases<sup>8-10</sup>. Little is known about the clinical presentation, imaging  
45 findings and outcome in dogs, potentially stalling diagnosis and subsequent treatment. To the  
46 authors' knowledge, this is the first case series specifically evaluating the clinical features of  
47 intracranial empyema in dogs from multiple sources with the aim of describing its presentation,  
48 diagnostic imaging findings, treatment options and outcome. The aim is that by detailing such  
49 cases, we will attain a better understanding of the condition to allow owners to make a more  
50 informed decision regarding treatment.

## 51 Materials and Methods

52

53 Medical records from two referral centers between December 2008 and November  
54 2015 were searched to identify dogs that had been diagnosed with intracranial empyema. To  
55 be included in this study, dogs had to fulfill 1 or more of the following 3 inclusion criteria: a  
56 magnetic resonance imaging (MRI) scan with space occupying accumulation of extra-axial  
57 material suggestive of empyema, a CSF analysis suggestive of empyema, or direct visualization  
58 of purulent material during intracranial surgery. Dogs that received surgical, medical, or both  
59 forms of treatment were included. Dogs were excluded from the series if medical records or  
60 imaging studies were incomplete or unavailable for review or if a final diagnosis of intracranial  
61 empyema could not be reached. This study was approved by the clinical ethical research  
62 committee board of the Royal Veterinary College RVC (reference number 2016 1526B)

63

64 Information retrieved from the medical records included signalment, history, general  
65 physical and neurological examination findings, concurrent medical conditions, imaging  
66 findings, CSF cytology, culture and sensitivity results, treatment administered, surgical  
67 procedure if performed, presence of complications and short term outcome.

68

69 All dogs were anesthetized and MRI scans were performed using a 1.5 or 0.4 Tesla  
70 scanner (Intera; Philips Medical Systems or Aperto, Hitachi Medical Corporation, Tokyo,  
71 Japan) or a CT scan using a 16 multi detector row unit CT scanner (Mx8000 IDT, Philips, Best,  
72 the Netherlands). Anesthetic protocols differed among dogs, premedication with methadone  
73 (0.2mg/kg IV), anesthetic induction with propofol (1mg/kg IV and then to effect) and  
74 maintenance of anesthesia with sevoflurane in oxygen was a frequently used protocol. All  
75 imaging series were available for review and comprised a minimum of T2-weighted, T1-  
76 weighted and T2-weighted FLAIR sequences and included transverse, sagittal and dorsal

77 images, with T1-weighted images acquired before and after IV administration of gadolinium  
78 contrast agent (0.1 mmol/kg gadoterate meglumine, Dotarem ®; Guerbet, Milton Keynes, UK  
79 or 0.05 mmol/kg gadobenate dimeglumine, Multihance ®; Bracco, Milan, Italy). All imaging  
80 studies were reviewed for diagnostic accuracy by two board certified neurologists (SDD and  
81 IP) and a residency trained radiologist (SG) and only those cases with imaging features  
82 consistent with intracranial empyema were included in the study. These features include the  
83 presence of extra-axial material that is T1 weighted hypointense, T2 weighted hyperintense  
84 with peripheral or heterogenous contrast enhancement together with contrast enhancing  
85 meninges.

86

87 CSF analysis was performed in selected cases (cisternal: total nucleated cell count  
88 ((TNCC) <5 cells/ $\mu$ l)), total protein (TP) 25mg/dl)). Owners were informed of the findings and  
89 the treatment options were discussed with a board-certified veterinary neurologist or resident  
90 in a veterinary neurology training program. The final decision for medical or surgical treatment  
91 or euthanasia was made by the owner of each dog.

92

93 Short-term outcome was defined as the period immediately following intervention up  
94 to the point of discharge and re-examination visits 4-6 weeks following treatment. Long-term  
95 outcome was obtained initially via telephone conversation with the referring veterinary  
96 surgeons. For dogs that were deceased, date and cause of death, as well as the last documented  
97 neurological status were recorded. Conforming to hospital ethics and welfare committee  
98 guidelines, only owners of dogs that were confirmed alive at the time of data collection were  
99 subsequently contacted. Owners were posted a letter with study details and a standardized  
100 questionnaire that had been reviewed and approved by the hospital ethics and welfare  
101 committee. Telephone interviews were conducted using the questionnaire, which included

102 questions covering the patients' quality of life, neurological status, any long term medication  
103 and overall response to treatment.

104

## 105 Results

106

107           Nine dogs with a median age of 3.5 years (range 4 months-12.5 years) were included  
108 in this study (Table 1). Four dogs were male (one neutered) and five were female (two neutered).  
109 Breeds included Labrador Retriever (n = 1), King Charles Spaniel (n = 2), Cocker Spaniel (n  
110 = 1), Jack Russell Terrier (n = 1), Golden Retriever (n = 1), Hungarian Vizsla (n = 1) Bassett  
111 Hound (n = 1) and a cross breed (n = 1). All dogs presented with an acute onset of progressive  
112 clinical signs and seven of the nine dogs had been placed on antibiotics prior to referral. Despite  
113 seven of these dogs receiving empirical antibiotics prior to presentation, no improvement was  
114 seen and their signs continued to progress. Duration of clinical signs varied from 1 to 4 days  
115 (median 3 days, mean 2.8 days). General physical examination revealed abnormalities in six  
116 dogs, including a heart murmur (n=3 dogs), chronic dermatitis/otitis externa (n=1),  
117 submandibular lymphomegaly (n=2), pain on opening of the jaw (n=2) and pyrexia (n=2 dogs).  
118 Indications of a potential primary source of infection were observed in six dogs. This included  
119 unilateral exophthalmos (n=3), craniofacial wounds (n=2) and otitis externa (n=1).

120

121           Neurological examination revealed abnormalities in seven dogs, which included  
122 obtundation (n=5), postural reaction deficits (n=5), and cranial nerve deficits (n=5). Two of  
123 these dogs had experienced generalized tonic-clonic seizures prior to presentation. The two  
124 dogs without neurological deficits presented for further evaluation of unilateral exophthalmos.

125

126           Six dogs had complete blood cell counts performed on admission, two of which were

127 unremarkable, with abnormalities including neutrophilia (n=2), lymphocytosis (n=1) and mild  
128 anemia (n=1). Biochemistry was also performed in six dogs with no abnormalities identified.  
129 Three dogs did not have complete blood cell counts or biochemistry performed at the time of  
130 admission but did have venous blood gas analysis and blood smear evaluation performed with  
131 no abnormalities detected. Urinalysis was performed in one dog which revealed moderate  
132 hematuria and proteinuria with a negative bacterial culture. Thoracic radiography (n=1) and  
133 abdominal ultrasonography (n=1) were unremarkable. Echocardiography was performed in the  
134 three dogs with heart murmurs, two of which were consistent with mitral valve disease and the  
135 third with a congenital defect affecting the aortic valve. One dog had an ocular ultrasound  
136 which revealed signs consistent with retrobulbar cellulitis. Two dogs had ophthalmic  
137 examinations by board certified ophthalmologists with one having age related nuclear sclerosis  
138 and cataracts and the other having conjunctival hyperemia, exophthalmos and third eyelid  
139 protrusion.

140

141 All dogs had advanced imaging performed within 24 hours of presentation. Eight of the  
142 nine cases underwent MRI of the head with one case undergoing cranial CT. MRI revealed the  
143 presence of extra-axial material, which appeared T1 weighted hypointense (n=6) or isointense  
144 (n=2) and T2 weighted hyperintense (n=8) to grey matter. On fluid attenuation inversion  
145 recovery images (FLAIR) the material had a heterogenous intensity (n=5) or was hyperintense  
146 (n=3) to grey matter. In two cases the material was extensive and compressing half of the  
147 cerebral cortex, with the remaining cases having material compressing one or more of the  
148 frontal lobes (n=2), the parietal lobe (n=1), the olfactory lobe (n=2), the cerebellum (n=2), the  
149 brainstem (n=1), the thalamus (n=1) and the temporal lobe (n=1), with the location often  
150 dictated by the source of infection. In seven of the eight cases the material appeared subdural  
151 in nature as it was crescent in shape and crossing suture lines. Perilesional edema was identified



152 in four of the eight cases. A degree of osteomyelitis was identified in five cases, affecting the  
153 frontal bone (n=3), the temporomandibular joint and calvarium (n=1) and the sphenoid bone  
154 (n=1). The material was contrast enhancing with peripheral (rim) enhancement (n=5) or  
155 heterogenous contrast enhancement (n=3). Meningeal enhancement was also evident in all  
156 cases and was predominantly dural in nature (n=8) with some dogs also having a degree of  
157 leptomenigeal enhancement as well (n=5). Five of the eight cases had evidence of mass  
158 effect in the form of midline shift (n=5), ventricular compression (n= 3), foramen magnum  
159 herniation (n=2) and caudal transtentorial herniation (n=1). (Figures 1 and 2). The  
160 neuroanatomical localization following examination of forebrain (n=5) and central vestibular  
161 syndrome (n=2) was consistent with the lesion location on MRI in all cases. In the two dogs  
162 that had a history of generalized seizure activity, the empyema identified on MRI was affecting  
163 the right side of the cerebrum in one dog and the left thalamus and left temporal lobe in the  
164 other dog.

165

166 CSF analysis was performed in two cases and the first revealed a pleocytosis (35%  
167 neutrophils; 40% monocytes/macrophages) with a TNCC of 260 cells/ $\mu$ l and total protein of  
168 59 mg/dl. The cytology revealed occasional degenerate neutrophils, rarely containing very  
169 small coccoid structures and thin rod like structures. The structures identified were not  
170 convincing enough to definitively confirm intracellular bacteria and unfortunately this sample  
171 was not sent for culture. The second case did not have sufficient sample for a total nucleated  
172 cell count but did have a protein of 475 mg/dl and cytology consistent with a neutrophilic  
173 pleocytosis. The neutrophils varied from mature to variably karyolytic, frequently having  
174 phagocytosed the bacteria which were mature small diplococcoid in nature. Culture of the latter  
175 revealed a moderate growth of *Streptococcus pneumoniae*.

176

177           Following the suspected diagnosis of intracranial empyema, six of the cases had  
178 surgical intervention either in the form of a single craniectomy (n=4), multiple small  
179 craniectomies (n=1) or a total ear canal ablation and lateral bulla osteotomy (n=1). Of those  
180 dogs that had intracranial surgery, two had a transfrontal approach and three a rostral tentorial  
181 approach, with the mean surgery time being 136 minutes (range:110-185mins). A durotomy  
182 was performed, which was followed by extensive lavage with saline before closure. A  
183 cranioplasty was not performed in any of the cases (Figure 3). Purulent fluid was seen and  
184 sampled for bacterial culture in all surgically treated cases. Of the 5 dogs that underwent a  
185 craniectomy, a neurological decline was not seen in any following the surgery; 2 remained  
186 neurologically normal, 2 remained neurologically static, and 1 experienced an immediate  
187 neurological improvement following surgery.

188

189           Of the remaining three cases, one was medically managed in the form of intravenous  
190 antibiotics administration and supportive care. Enrofloxacin and amoxicillin clavulanic acid  
191 were administered intravenously for 10 days before changing to oral enrofloxacin and  
192 amoxicillin clavulanic acid. This medically managed case had not received any antibiotics prior  
193 to referral and the decision to medically manage this case was owner driven, as they did not  
194 want any further invasive diagnostic or treatment modalities. The remaining 2 were euthanized  
195 immediately after diagnosis without treatment attempted. Of those dogs that underwent  
196 treatment (either medical or surgical), 4 of 7 had treatment initiated within 24 hours of  
197 presentation, 2 of 7 had treatment initiated within 36 hours of presentation, and 1 of 7 had  
198 treatment initiated within 48 hours of presentation.

199

200           Seven cases had one or more samples sent off for culture and sensitivity from surgery  
201 (n=5), fine needle aspirate (FNA) of an intra-oral lesion (n=1), CSF (n=1) or an ear swab (n=1).

202 From these samples, five returned with no bacterial isolates, one returned with *Enterococcus*  
203 (surgical swab), one with *Streptococcus pneumoniae* (from CSF) and one with coagulase  
204 positive *Staphylococcus* (ear swab). Seven of the nine dogs received antibiotics prior to referral  
205 which included the two dogs with positive cultures. Four of the five dogs that had surgical  
206 samples taken for culture were already on antibiotics, and the one that hadn't received any  
207 antibiotics returned with no bacterial isolates.

208

209 All cases received antibiotics with seven cases being on at least two different types of  
210 antibiotics (Table 1). Antibiotics were initially given intravenously and subsequently changed  
211 to oral administration. Antibiotics were administered intravenously for between 2 and 10 days  
212 (mean 5 days, median 4 days) before being changed to oral administration. The median  
213 antimicrobial course length was 6 weeks (range 2 – 28 weeks). Some dogs received a short  
214 course (48 hours) of intravenous corticosteroids (n=2 (0.1-0.3mg/kg IV; Colvason; Norbrook  
215 0.2%w/v)). Administration of intravenous mannitol was considered on an individual basis with  
216 bolus administration in case of suspected increased intracranial pressure. A total of four dogs  
217 were administered mannitol (n=4 (0.3-0.5g/kg IV)), with three receiving a single dose during  
218 the surgical procedure and the fourth dog receiving a dose during surgery and 48hours and 72  
219 hours post-operatively. The latter was administered the extra doses of mannitol due to concerns  
220 that the dog was showing clinical signs suggestive of increased intracranial pressure. All four  
221 dogs that received mannitol had evidence of increased intracranial pressure on their MRI scans.

222

223 Seven out of the nine dogs survived to discharge, with the median time hospitalized  
224 being 7 days (range 4-10 days), with the one case medically managed being hospitalized for  
225 10 days. One dog developed a corneal ulcer whilst hospitalized, which was medically managed  
226 with topical medication to which it responded to well. A neurological improvement was seen

227 within 24 hours (n=5), 48 hours (n=1) and within 72 hours (n=1) following intervention. At  
228 the time of discharge, three of the dogs were neurologically normal and the other four, whilst  
229 still showing neurological deficits (cranial nerve deficits n=3; postural deficits n=2; head tilt  
230 n=1), had all shown a neurological improvement. The two that did not survive to discharge  
231 were euthanized at the time of diagnosis without treatment attempted. One dog was euthanized  
232 under general anesthetic following the MRI scan with no reason given as to why treatment  
233 wasn't pursued, despite treatment being offered. The second dog was euthanized as the owners  
234 did not want to proceed because of an uncertain prognosis together with a lack of guarantee  
235 the dog would regain a good quality of life. Whilst the two euthanized dogs were neurologically  
236 abnormal at the time of presentation (similar to the other dogs in this series), nothing could be  
237 identified on their MRI scans or clinical notes that would have given a suggestion that these  
238 two dogs were precluded from having a similar outcome as the other dogs in this series if  
239 treatment was attempted.

240

241         Given the external signs evident on clinical examination, together with the advanced  
242 imaging findings, the routes of infection were suspected to be intra-oral (n=2), retro-bulbar  
243 (n=3), external trauma (n=2) and otogenic (n=2). For the two cases suspected to be intra-oral  
244 in nature, lesions were identified in the mouth when both patients were induced for anesthesia.  
245 Subsequent MRI revealed one to have an abscess involving the temporomandibular joint  
246 extending intra-cranially through the skull and the other revealed signs consistent of contiguous  
247 infection extending to the sphenoid bone and in towards the left temporal lobe at the level of  
248 the thalamus. One of the otogenic cases had underwent a total ear canal ablation and lateral  
249 bulla osteotomy 6 months prior to presentation on the same side as the empyema.

250

251           Of the seven cases that survived to discharge, we attained long term follow up for six  
252 (Table 1). Four of the six were still alive at the time of writing with all four being neurologically  
253 normal and free of clinical signs according to the owners and the referring veterinary surgeons.  
254 None of the dogs were on any long term treatment nor experienced recurrence of clinical signs.  
255 The two remaining dogs were euthanized for unrelated reasons. One was euthanized 3 years  
256 following surgery for gastrointestinal disease and the other was euthanized 17 months  
257 following diagnosis due to congestive heart failure. At the time of death, both cases were  
258 neurologically normal other than one dog retaining a mild head tilt according to the referring  
259 veterinary surgeons.

260

## 261 Discussion

262

263           Intracranial empyema is a neurological emergency that once diagnosed, requires rapid  
264 and aggressive intervention. For an owner, making decisions regarding treatment can be  
265 challenging given the expensive and invasive nature of surgical intervention and the  
266 uncertainty of the prognosis. To the authors knowledge, this is the first case series in the  
267 veterinary literature evaluating the clinical presentation, diagnostic findings, treatment and  
268 outcome of dogs diagnosed with intracranial empyema.

269

270           This case series highlights the differing presentations and underlying causes of  
271 intracranial empyema in dogs. The presumed sources of infection in this case series comprised  
272 otogenic, traumatic, retrobulbar and intra-oral extensions of infection. Interestingly, whilst  
273 sinusitis, otitis and skull trauma are amongst the most common sources of infection for human  
274 subdural empyema, the most common current etiology is subsequent to a neurosurgical  
275 procedure such as surgical evacuation of a subdural haemorrhage<sup>8,11</sup> It is possible with the

276 continued advancement of veterinary neurology coupled with increasingly performed  
277 intracranial surgery, there is the potential to see intracranial empyema more commonly as a  
278 complication following veterinary neurosurgical procedures.

279

280         Despite these variations within a particular condition, a consistent finding was the acute  
281 and progressive nature of the clinical signs. A previous study investigating otogenic  
282 intracranial infection categorized the onset of neurologic dysfunction into acute (1-48 hours),  
283 subacute (3-7 days) or chronic (> 7days), with the majority of the patients in that series having  
284 a chronic onset<sup>2</sup>. Elsewhere in the veterinary literature, the onset of neurological signs in cases  
285 with intracranial empyema have varied with some being acute, subacute or chronic in nature<sup>1</sup>,  
286 <sup>25</sup>. In our series, the duration of clinical signs varied from 1 to 4 days (median 3 days, mean 2.8  
287 days). If we were to categorize similarly to the previous study, then 4/9 would be classed as  
288 acute and 5/9 would be subacute. It is possible that certain origins of empyema are associated  
289 with an acute onset of neurological signs. This hypothesis however needs further investigation  
290 in future studies. Another striking finding of this case series was despite the severity of the  
291 presenting clinical signs, the majority of those cases in which treatment was attempted resulted  
292 in a good outcome. Only one of the cases presented in this series was medically managed, the  
293 majority being surgically treated. Although being presented with a dog with intracranial  
294 empyema can be overwhelming and stressful, our findings suggest that rapid and aggressive  
295 intervention can result in a successful outcome.

296

297         Although intracranial empyema is a manifestation of an infectious disease, general  
298 physical examination findings and ancillary diagnostics, such as a complete blood count,  
299 biochemistry, urinalysis, echocardiography, and abdominal and thoracic imaging did not reveal  
300 clear indications of a more generalized infectious process. For all dogs in which treatment was

301 attempted, one or more samples were submitted for bacterial culture and sensitivity testing.  
302 However only three of a total of eight samples returned culture positive, one each from a  
303 surgical swab, ear swab and CSF sample. Previous literature in the subject has suggested that  
304 culturing from CSF is not normally rewarding and CSF analysis itself is often not specific for  
305 bacterial abscessation<sup>7,12,13</sup>. Whilst the ear swab and CSF positive cultures were from the same  
306 dog, it was considered unlikely the ear swab isolate was the cause of the intracranial empyema.  
307 The fact that different isolates were cultured should not be considered surprising given that in  
308 dogs with otitis media, cultured samples from the horizontal ear canal and the middle ear have  
309 been reported to demonstrate different results in 89.5% of ears<sup>24</sup>. Culture directly from the  
310 surgical site was positive in just one of the five cases that had sampling from that site in this  
311 case series, and this particular case was already receiving antibiotics. A possible explanation  
312 for this could be due to the fact that the majority (7/9) of cases were placed on antibiotics prior  
313 to referral, which has previously been discussed in the literature<sup>6,13</sup>. Blood culture was not  
314 attempted in any of these dogs but could potentially be considered as an additional ancillary  
315 diagnostic in dogs with intracranial empyema given its use in other neurological disorders such  
316 as discospondylitis and spinal epidural empyema<sup>22,23</sup>.

317

318         Appropriate surgical aftercare is a key component in order to successfully treat dogs  
319 with intracranial empyema. Most surgically treated dogs underwent a craniectomy, after which  
320 not only the basic principles of post-operative aftercare were adhered to but specific  
321 recommendations of care following intra-cranial surgery were considered. The use of  
322 corticosteroids in patients with intracranial empyema remains a contentious issue,  
323 demonstrated by the fact that only two of the nine dogs in this case series were administered  
324 corticosteroids. Corticosteroids have been administered to the majority of reported cases in the  
325 veterinary literature<sup>2,25,26</sup>. It is thought antibacterials administered to these patients induce

326 cellular destruction of bacteria and subsequent lipopolysaccharide liberation, leading to the  
327 initiation of a cascade of inflammatory events<sup>14,15</sup>. However, It is suggested that  
328 dexamethasone early in the treatment of bacterial meningitis, decreases the inflammatory  
329 response associated with the release of bacterial cell material<sup>16,17</sup>. In the human literature, the  
330 results are inconclusive, with previous reports supporting the use of short term anti-  
331 inflammatory doses of corticosteroids in people with bacterial meningitis, as they are beneficial  
332 in lowering intracranial pressure and reducing CNS inflammation<sup>27</sup>. However a recent  
333 systematic meta-analysis examining the use of adjunctive dexamethasone in patients with  
334 bacterial meningitis failed to suggest a clear benefit<sup>28</sup>.

335

336 It remains unclear how long dogs with intracranial empyema should be kept on  
337 antibiotics for. In the absence of positive bacterial culture and sensitivity results, a broad  
338 spectrum, bactericidal antimicrobial with the ability to cross the blood-brain barrier and reach  
339 adequate concentrations in the central nervous system should be considered the ideal choice<sup>12,13</sup>.  
340 Whilst the majority of patients in this case series were placed on two different antibiotics,  
341 amoxicillin clavulanic acid was the most commonly used. Whilst this is a broad spectrum  
342 antimicrobial, it does not cross the blood-brain barrier effectively. It is however not completely  
343 clear how important the ability to cross the blood-brain barrier truly is in patients with  
344 intracranial empyema. It can indeed be assumed that animals with such severe brain pathology  
345 do no longer have an intact blood-brain barrier, allowing penetration of antimicrobials that  
346 might otherwise be restricted<sup>10,18</sup>. A further consideration is the fact that the majority of the  
347 empyema in this case series was epidural or subdural in nature and hence outside the blood-  
348 brain barrier. Enhancement following intravenous contrast administration was a consistent  
349 finding on MRI, further illustrating the questionable importance of blood-brain barrier  
350 penetration for antibiotics administered in patients with intracranial empyema. Whilst there is



351 no consensus on the length of antimicrobial therapy for these patients, demonstrated here by  
352 the wide range of 2-28 weeks, it is generally accepted that antibiotics should be initially  
353 administered intravenously followed by an oral course long term<sup>19</sup>.

354

355         The median age of dogs in this case series was 2 years, with four of the nine dogs being  
356 less than 12 months old. This is consistent with the human literature where the majority of  
357 patients with intracranial empyema are between 10-20 years old<sup>20,21</sup>. Whether these dogs have  
358 a more immature immune system or are more prone to traumatic episodes is unclear. Although  
359 this finding could indeed suggest a predisposition for younger animals to suffer from  
360 intracranial empyema, a larger sample size would be needed to evaluate this hypothesis.

361

362         Whilst the MRI characteristics of intracranial empyema have previously been  
363 described<sup>1,2,5</sup>, this is the first case series focusing on intracranial empyema in dogs from  
364 multiple different sources of infection. Generally, the empyema was subdural (occasionally  
365 epidural) in nature, T1 weighted hypointense and T2 weighted hyperintense with peripheral or  
366 heterogenous contrast enhancement. Evidence of concurrent osteomyelitis and a degree of  
367 mass effect was identified in individual cases. These MRI characteristics when considered  
368 together with the history and clinical signs of the patient can be considered suggestive of  
369 intracranial empyema. In differentiating subdural empyema from a subdural hematoma, you  
370 might expect the latter to potentially be more isointense to brain parenchyma on T2 weighted  
371 images, lack a contrast enhancing rim and one might also expect the presence of signal void on  
372 T2\* weighted images<sup>26</sup>.

373

374         This study is obviously limited by its retrospective nature, which restricted standardized  
375 patient assessment and treatment. Standardization of patient care was further limited by the

376 heterogeneous nature of included cases. Despite including animals over a 7-year period from  
377 two busy referral centers, only 9 dogs could be included. Although this could be considered a  
378 limitation of the study, this finding is most likely a reflection of the rare nature of intracranial  
379 empyema in dogs. Despite the small number and heterogeneous character of included cases,  
380 several clinically important conclusions can be drawn from this study. Intracranial empyema  
381 in dogs is rare, but can present as a neurological emergency that requires rapid and aggressive  
382 treatment. Affected dogs can present neurologically normal and the majority of patients do not  
383 demonstrate evidence of systemic disease on general physical examination or ancillary  
384 diagnostics. Treatment of intracranial empyema seems to be associated with excellent  
385 outcomes and a rapid recovery. Further studies are needed to evaluate the most appropriate  
386 type of surgical aftercare, type and duration of antibiotic treatment.

387

388

389

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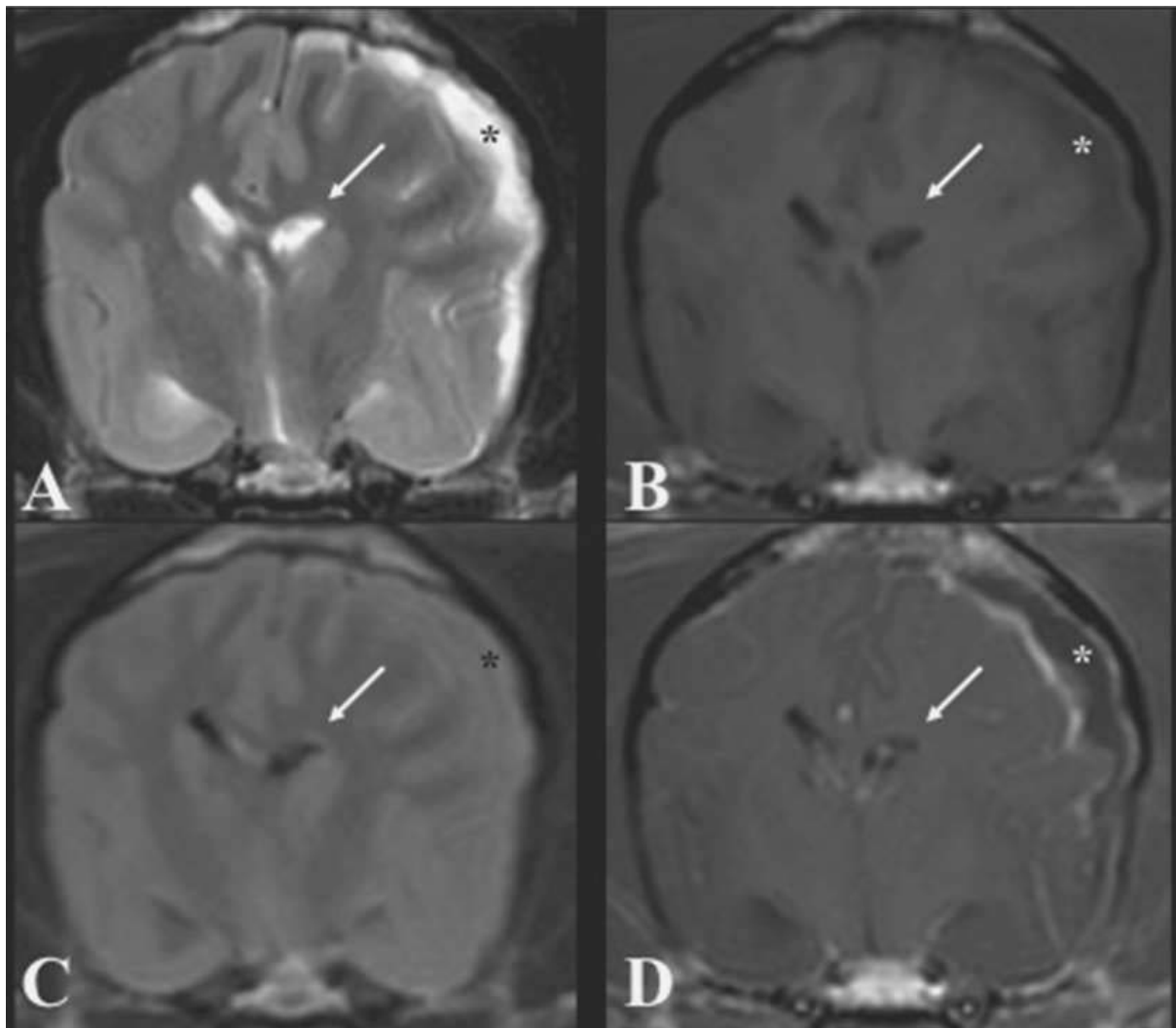
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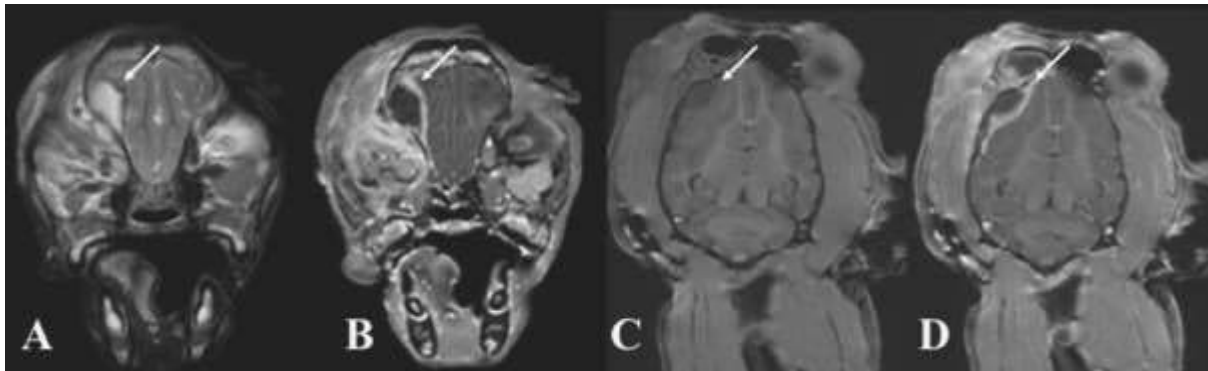
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## 456 Figure legends

457 Figure 1: MRI of a 7 year male entire Jack Russell Terrier with subdural empyema. The images  
458 show a T2weighted (A), T1weighted (B), T2weighted FLAIR (C) and T1weighted after IV  
459 administration of gadolinium based contrast (D) transverse images of the brain at the level of  
460 the thalamus. There is accumulation of extra-axial, crescent shaped, T2weighted hyperintense,  
461 T1weighted hypointense material compressing the left cerebral hemisphere (asterisk). The  
462 material does not suppress on FLAIR (C) and following gadolinium administration there is a  
463 peripheral enhancement of the material (D) and both dural and leptomeningeal diffuse contrast  
464 enhancement. There is a degree of midline shift and compression of the lateral ventricle (white  
465 arrow).



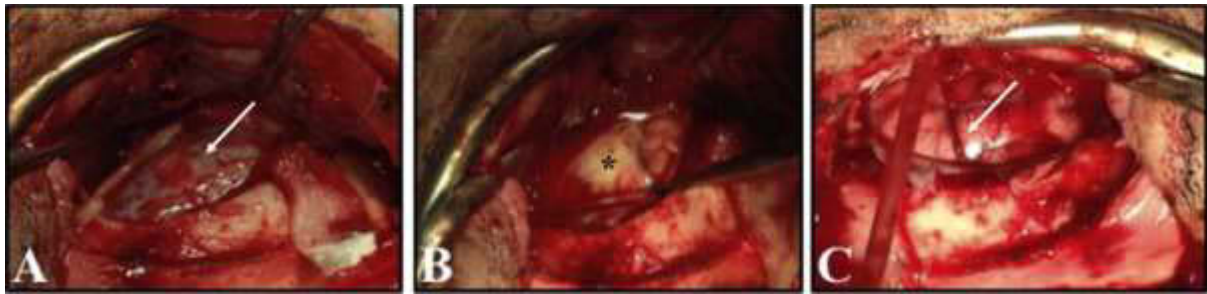
467 Figure 2: Transverse T2weighted (A), transverse T1weighted after IV administration of  
468 gadolinium based contrast (B), dorsal T1weighted (C) and dorsal T1weighted after IV  
469 administration of gadolinium based contrast (d) MR images of a 6-month old crossbreed with  
470 intracranial empyema. Accumulation of extra-axial, lentiform, T2weighted hyperintense,  
471 T1weighted hypointense material adjacent to the frontal and parietal lobes on the right hand  
472 side (white arrow). Following gadolinium there is a peripheral enhancement of the material  
473 (B and C) and there is a degree of midline shift to the left. There is also a degree of  
474 osteomyelitis (A and B: asterisk) with T2 weighted hyperintense thickening of the periorbital  
475 and retrobulbar tissues of the right eye. The right frontal sinus also contains hyperintense  
476 material together with a degree of mucosal thickening.



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479 Figure 3: Rostrotentorial craniectomy in a 6 month old female entire Labrador retriever with  
480 subdural empyema secondary to a retrobulbar infection. A) Following the craniectomy, the  
481 intact dura is visible but appears discolored (white arrow). B) The dura has been incised and  
482 the empyema is visible in situ (asterisk). C) Following an intraoperative swab for culture and  
483 sensitivity, the empyema is removed and flushed with copious amounts of saline, with normal  
484 brain parenchyma now visible (white arrow).



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