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# Can Cytosine Arabinoside With Prednisolone Treatment for Canine Meningoencephalitis of Unknown Origin Increase Survival Time Compared to Prednisolone Treatment Alone?

A Knowledge Summary by

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# KNOWLEDGE SUMMARY

**PICO question**

In treatment of canine patients with meningoencephalitis of unknown origin (MUO), is combination therapy of cytosine arabinoside (CA) with prednisolone more effective than prednisolone as a sole therapy at increasing survival time?

**Clinical bottom line**

Based on current available evidence, cytosine arabinoside with prednisolone has greater median survival time than prednisolone as a sole therapy in dogs with meningoencephalitis of unknown origin. The evidence to support this is very weak, as there are currently a low number of published papers with a relatively small number of cases reported in these studies evaluating cytosine arabinoside with prednisolone or prednisolone as a sole therapy for treatment of meningoencephalitis of unknown origin.

## Clinical scenario

You are presented with a 4-year-old male neutered Boston Terrier with a five day history of seizures, progressive mentation changes and compulsive circling. The patient has had no previous ailments or been on any previous treatments. Multifocal intensities were noted within the forebrain on MRI (T2-weighted). Mixed mononuclear pleocytosis with increased protein concentration was noted on cerebrospinal fluid (CSF) examination. Negative serology and CSF titres for *Neospora caninum* and *Toxoplasma gondii* were performed. A provisional diagnosis of MUO is made for which you want to start treatment soonest, but you are unsure of the effectiveness of using a combination of cytosine arabinoside with prednisolone compared with prednisolone alone.

## The evidence

There is limited available evidence for treating MUO involving CA in combination therapy with prednisolone or prednisolone alone. Five studies were located examining the effect of CA in combination with prednisolone, with a relatively small number of cases reported in each of these. Only one paper was identified studying the use of prednisolone alone for treatment of MUO. The available evidence is weak as five studies were case series, with high likelihood of bias, the inability to detect much of the bias, and the inability to estimate a treatment effect. A repeat literature search involving different chemotherapeutic treatment options for MUO could be beneficial. Whilst there is no direct comparison between these two treatment options, CA with prednisolone had greater actual and estimated median survival time than prednisolone as a sole therapy in dogs with MUO.

## Summary of the evidence

| **Lowrie** (2016) | |
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| **Population:** | Dogs with presumptive MUO presenting to the small animal neurology service at Davies Veterinary Specialists between May 2006 and August 2015. |
| **Sample size:** | 80; 39 historical control from Lowrie *et al* (2013) treated with subcutaneous (SC) CA, 41 prospectively recruited to receive continuous rate infusion (CRI) CA. |
| **Intervention details:** | • The CRI CA dogs received a neurologic examination, |

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| | complete blood count (CBC), serum biochemistry profile, serum antibody titres to *Neospora caninum* and *Toxoplasma gondii*, brain MRI, CSF analysis. The SC CA control group received the same with the exception to testing for *Toxoplasma gondi*.<br>• Both groups were treated with a standard protocol for immunosuppressive doses of oral prednisolone (1mg/kg twice daily (BID) with tapering doses after 4 weeks). This was reduced to 0.5mg/kg BID for 6 weeks, then 0.25mg/kg BID for 6 weeks, then 0.25mg/kg once daily for 6 weeks, then 0.25mg/kg every 48hours for 6 weeks followed by 0.25mg/kg every 72 hours for 6 weeks.<br>• Dogs in the historical control group (Lowrie *et al* 2013) received subcutaneous CA at 50mg/$m^2$ every 12 hours for 2 days repeated every 3 weeks before increasing the treatment intervals by a week every 4 treatment cycles.<br>• Dogs prospectively recruited received CA CRI at 100mg/$m^2$ over 24 hours. They then received 50mg/m2 SC CA every 12 hours for 2 days every 3 weeks for 3 cycles before increasing the treatment by a week every 4 treatment cycles.<br>• Repeat MRI and CSF analysis at 3 months following the start of treatment for the prospectively recruited CRI group and historical SC group. |
| **Study design:** | Prospective cohort study with historical control group |
| **Outcome studied:** | The effect of a CA CRI on mortality in dogs with MUO and compare CA CRI to CA SC.<br><br>Objective:<br>• Mortality at 3 months (dogs that died or were euthanised were recorded and survival was compared as a binary value with a group of historical control dogs).<br>• Occurrence of MRI and CSF abnormalities at follow-up. |
| **Main findings: (relevant to PICO question):** | • Mortality of 4/41 (10%) in CA CRI group (compared with 22/39 (56%) with in CA SC group) at 3 months. Log rank analysis of the Kaplan-Meier survival curves represented a significantly better survival with CA CRI. All dogs alive at 3 months in both groups were alive at 12 months.<br>• 34/37 surviving dogs in the CRI group had a normal MRI scan at 3 months compared with 7/17 surviving dogs in the SC group (statistically significant difference between the groups).<br>• CSF was normal in a significantly higher proportion of dogs in the CA CRI group (36/37) compared to the SC group (10/17). |
| **Limitations:** | • Historical control data gathered at a different time period from a different study. |

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| | • Patients not followed up until death or euthanasia for survival.<br>• Dogs with a more aggressive form of inflammatory CNS disease were excluded from the study (focal cortical hyperintense lesions on MRI T1-W1) as they were likely to represent necrotizing encephalitis, which may affect survival and mortality analysis.<br>• Comparative dosage of the treatments was not equal.<br>• Diagnosis of MUO was presumptive. |

| **Lowrie** (2013) | |
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| **Population:** | Dogs with clinically confirmed MUO presenting to the small animal neurology service at Davies Veterinary Specialists between May 2006 and August 2011. |
| **Sample size:** | 39 |
| **Intervention details:** | • All dogs received a neurologic examination, complete blood count, serum biochemistry profile, serum antibody titres to Neospora caninum, brain MRI, CSF analysis.<br>• All dogs were treated with a standard protocol initiated with immunosuppressive doses of oral prednisolone; 1mg/kg twice daily (BID) with tapering doses after 4 weeks to 0.5mg/kg BID PO for 6 weeks, followed by 0.25mg/kg BID for 6 weeks, followed by 0.25mg/kg once daily (SID) for 6 weeks, followed by 0.25mg/kg every 48 hours for 6 weeks, followed by 0.25mg/kg every 72 hours for 6 weeks.<br>• Dogs received subcutaneous CA at 50mg/m$^2$ every 12 hours for 2 days repeated every 3 weeks for 4 cycles, before decreasing the frequency at the same dose to every 4 weeks for 4 cycles, then every 5 weeks for 4 cycles followed by every 6 weeks for 4 cycles.<br>• Repeat MRI and CSF analysis at 3 months following the start of treatment. If abnormal the treatment regime was altered accordingly to prolong treatment. If a relapse occurred the protocol was restarted. |
| **Study design:** | Prospective case series |
| **Outcome studied:** | Prognostic factors and outcome of dogs with MUO using a standard treatment protocol<br><br>Subjective:<br>• Long-term follow-up of more than 18 months after diagnosis when treatment was anticipated to have been discontinued. Defined by owner/referring vet as either excellent if all treatment discontinued and normal, good if the dog remained on treatment and was normal and poor if the dog was on treatment but abnormal (assessed at re-exam or |

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| | phone consultation with referring vet or owner).<br>Objective:<br>• Relapse with recurrence of neurologic signs suspected or confirmed with MRI with an increase in seizure frequency of over 50% (however if controlled to under 50% of seizure frequency at time of initial presentation with or without anti-epileptic treatment then a relapse was not suspected).<br>• Occurrence of MRI and CSF abnormalities at 3 month follow-up.<br>• Mortality rate. |
| **Main findings: (relevant to PICO question):** | • 22 dogs died or were euthanised following diagnosis of MUO (13 within 0-3 days, 3 in 4-14 days and 6 between 15 and 52 days). Median survival time following diagnosis in all deceased dogs was 2 days (range 0-52 days). Dogs that died did so within the first 3 months following diagnosis.<br>• Overall mean survival time was 26 days (range 0-2250 days).<br>• Survival was not affected by age at presentation, occurrence of seizures, CSF cell count or CSF protein concentration at initial diagnosis.<br>• Of the MRI features examined, evidence of foramen magnum herniation, loss of cerebral sulci and mass effect were all significantly associated with mortality.<br>• 17 dogs survived to 3 month re-examination. Repeat MRI and CSF collection was performed. All dogs alive at 3 months were still alive at 18 month follow-up.<br>• Long term follow up of surviving dogs ranged from 562 to 2250 days (median 1616 days).<br>• A good or excellent outcome was seen in 12/17 dogs with long-term follow-up; excellent in 7 dogs, good in 5 dogs and poor in 5 dogs.<br>• Relapse was recorded in 11/17 surviving dogs (median of 210 days following diagnosis, range 106-826 days) and was not significantly associated with outcome. |
| **Limitations:** | • No histopathological data to confirm type of meningioencephalitis.<br>• Dogs with optic form of GME were excluded from the study. |

| **Flegel** (2011) | |
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| **Population:** | Dogs presenting to Department of Small Animal medicine, University of Leipzig or Department of Clinical Neurology, University of Bern, between June 2000 and September 2008 with presumptive or diagnosed granulomatous meningoencephalitis (GME) or necrotizing (NME)/necrotizing leukocephalitis (NLE). |
| **Sample size:** | 43 dogs; 25 with GME and 18 with NME/NLE split into 1 of 2 treatment groups based on treatment received. Dogs with GME in group 1 (n = 14) treated with a combination of lomustine and prednisolone and group 2 (n = 11) treated with prednisolone alone. |

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| | Dogs with NME/NLE in group 3 treated with a combination of lomustine (n = 10) and prednisolone and group 4 treated with prednisolone alone (n = 8). |
| **Intervention details:** | • All dogs received a neurologic examination, complete blood count, serum biochemistry profile, serum antibody titres to *Neospora caninum*, *Toxoplasma gondii* and *Erlichia canis*, brain MRI, CSF analysis and antibodies against canine distemper in 19/25 dogs with GME. Some dogs received a needle brain biopsy for diagnosis of GME/NLE/NME otherwise it was considered a presumptive diagnosis of meningoencephalitis.<br>• All dogs were initially treated with 0.17-2.5mg/kg oral prednisolone twice daily immediately after diagnostic tests had been completed.<br>• 14 dogs with presumed or diagnosed GME and ten dogs with presumed or diagnosed NME/NLE were given oral lomustine (44 to 88mg/$m^2$ every 6 weeks) and prednisolone. Lomustine dose was reduced by 25% if leukopenia developed. Prednisolone dose was assessed every 6 weeks and reductions made in decrements of 20% (frequency of administration remained constant at twice daily) in the absence of neurological deficits, less than one seizure per month and clinicopathologic results analysis (CBC).<br>• 11 dogs with presumed or diagnosed GME and eight dogs with presumed or diagnosed NME/NLE were treated with prednisolone as a sole therapy. Dose reductions were attempted every 6 to 8 weeks (in decrements of 20% while maintaining dose frequency) in accordance with the absence of neurological deficits, under one seizure a month, assessed through a neurological examination or communication with the owner. In some instances owners made their own decision in reducing dosages. |
| **Study design:** | Retrospective cohort study |
| **Outcome studied:** | Comparing oral lomustine and prednisolone to prednisolone alone as for treatment of MUO.<br><br>Objective measured:<br>• Survival |
| **Main findings: (relevant to PICO question):** | • Diagnosis was confirmed in 8/25 GME dogs and 5/18 NME/NLE dogs. 2 dogs with GME and 2 dogs with NME/NLE via histologic examination of brain biopsy specimens and 6 GME dogs and 3 NME/NLE dogs at necropsy.<br>• 9/13 dogs that died in group 1 had documented cause of death; 3 due to recurrence of neurological signs and 6 due to non-neurologic conditions (renal failure, cardiac failure, hemorrhagic gastroenteritis, septic shock and suspected |

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| | liver failure).<br>• 5/8 dogs that died in group 2 had documented causes of death; 4 due to lack of improvement or relapse of neurologic signs and 1 due to chronic renal failure.<br>• All dogs in group 3 (8/8) had documented cause of death; 3 due to recurrence of neurologic signs and 5 due to other medical conditions (such as pleural effusion, cardiac failure, septic shock, gastrointestinal hemorrhage).<br>• 5/8 dogs reason for euthanasia was documented in group 4, all due to lack of improvement or relapse of neurologic signs.<br>• Median survival was 323 days (39-542 days) in dogs treated with prednisolone as a sole therapy with GME, and 457 days (107-709 days) in dogs treated with lomustine and prednisolone. No significant difference was found between these groups (1 and 2).<br>• Median survival was 91 days (7-494 days) in dogs treated with prednisolone as a sole therapy with NME/NLE, and 329 days (98-628 days) in dogs treated with prednisolone and lomustine. No significant difference was found between these groups (3 and 4).<br>• Reduction in median prednisolone dose per day within the first 12 months of treatment was seen in in dogs with GME treated with lomustine and prednisolone from 2.1 to 0.2mg/kg/day compared to 1.4 to 0.6mg/kg/day for dogs treated with prednisolone alone.<br>• Reduction in median prednisolone dose per day within the first 12 months of treatment was seen in in dogs with NME/NLE treated with lomustine and prednisolone from 1.9 to 0mg/kg/day compared to 2.1 to 1.0mg/kg/day for dogs treated with prednisolone alone.<br>• In 4 dogs with GME and 4 dogs with NME/NLE prednsisolone administration was able to be discontinued. In 3 of these GME affected dogs lomustine was also discontinued. |
| **Limitations:** | • No standard treatment protocol, differing dose ranges (including owners making decisions on tapering doses).<br>• Small number of cases, no power calculation performed.<br>• Diagnosis in (number) of dogs was carried out at post mortem. |

| **Smith** (2009) | |
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| **Population:** | Dogs presenting to Queen's Veterinary School Hospital, University of Cambridge between March 2004 and November 2006 with presumptive MUO. |
| **Sample size:** | 19 dogs split into 2 groups; group 1 treated with prednisolone in combination with vincristine and cyclophosphamide (n=10) and group 2 treated with prednisolone with cytosine arabinoside (n=9). Group 2 had 10 cases but one was retrospectively excluded for failing to meet the inclusion criteria. |

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| **Intervention details:** | • All dogs received a neurologic examination, serum antibody titres to *Neospora* and *Toxoplasma*, brain MRI or myelogram, CSF analysis, canine distemper virus testing (other individual specific tests if clinical suspicion including *Anaplasma phagocytophilum* and *Borrelia*).<br>• Dogs were randomly allocated to receive a low dose lymphoma 'COP' (COP- cyclophosphamide (oral 50mg/$m^2$ every 48 hours for 8 weeks, then the same regimen given over alternate weeks), vincristine (0.5mg/$m^2$ every 7 days for 8 weeks, then every 14 days) and prednisolone) protocol or the same dose of prednisolone (40mg/$m^2$ orally once daily) with the addition of CA. Intravenous (IV) CA was given once at the start of therapy over 24 hours at a total dose of 100mg/$m^2$. No further treatment of CA was given.<br>• In groups 1 and 2, oral prednisolone was reduced from 40mg/$m^2$ every 24 hours doe 7 days to 20mg/$m^2$ every 48 hours for 7 weeks, then the same regimen given in alternate weeks. The dose of prednisolone was tapered to suit individual requirements after 6 months and stopped if possible.<br>• Patients were followed for survival analysis and those alive at the time of writing were censored from survival estimate using an intention-to-treat analysis. The proportion of animal surviving 1 and 12 months was calculated excluding the censored cases in Kaplan-Meier analysis. |
| **Study design:** | Randomised control trial (double blinded) |
| **Outcome studied:** | Comparing COP lymphoma protocol to prednisolone with CA treatment for MUO<br><br>Objective:<br>• Survival analysis; Kaplin-Meier Analysis.<br>• Treatment failure analysis.<br>• Drug-related complications. |
| **Main findings: (relevant to PICO question):** | • For survival analysis three dogs were censored from group 2 including two that were euthanised for non-neurological disease (lymphoma and pneumonia) and one whose treatment was altered after a relapse (surviving for over a year receiving only prednisolone). Two were censored from group 1, both of whose treatment were stopped.<br>3 dogs were alive at time of writing in group 2 and 4 dogs in group 1, which were censored.<br>• Median survival was estimated at 1,063 days in dogs treated with prednisolone and CA (group 2). It was unable to be performed for group 1 because of the large number of censored cases.<br>• Intention-to-treat analysis showed a median survival time of 735 days (195-1274) in group 2 and 198 days (247-914) in |

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| | group 1.<br>• Proportion of animals surviving 1 and 12 months was calculated (excluding the censored cases) in Kaplan-Meier analysis leaving 7 animals in group 2 and 8 animals in group 1. 5/7 animals were alive at both 1 and 12 months in group 2, 5/8 animals were alive at 1 month and 4/8 were alive at 12 months for group 1.<br>• One animal in group 2 which worsened at day 40 but ultimately survived for 376 days (Kaplin-Meier plot of time-to-treatment failure with a median value of 1063 days in group 2 (102-2023)). |
| **Limitations:** | • Small population size. One case excluded from CA and prednisolone group due to CSF sample containing 90% neutrophils.<br>• Lack of follow-up and survival times.<br>• Two cases of possible infectious disease not ruled out due to severity of cases and need to start treatment.<br>• Confusing results - difficult to interpret survival analysis. In group 2, the removal of censored cases is unclear for the specific test and analysis (3 cases censored due to being alive and 3 due to euthanasia or treatment change). |

| **Menaut** (2008) | |
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| **Population:** | Dogs presenting to the National Veterinary School of Toulouse between September 2003 and January 2005 with presumptive or diagnosed MUO. |
| **Sample size:** | 11 |
| **Intervention details:** | • Dogs were selected based on treatment with a combination of steroids and CA.<br>• Covered some of the six criteria for MUO presumptive diagnosis including focal or multifocal central nervous system (CNS) signs, negative PCR and CSF analysis for infectious disease (distemper, neospora, toxoplasma, erlichiosis), CSF protein and white blood cell (WBC) analysis, CT signs consistent with MUO, ophthalmoscopy signs of optic neuritis, histopathological diagnosis.<br>• All dogs were treated with oral immunosuppressive prednisolone (1-2 mg/kg twice daily tapered over 3 months) and subcutaneous CA (50mg/$m^2$ every 12 hours for 48 hours repeated every 3 weeks). At week 28 the CA treatment interval was tried to be lengthened by one week every 4 weeks. Prednisolone dose was tapered from 2mg/kg twice daily (BID) for 1 week, to 1.5mg/kg BID for 1 week, then 1mg/kg BID for 1 week, then 0.75mg/kg BID for 1 week, then 0.5mg/kg BID for 2 weeks, then 1mg/kg every other day for 3 weeks, then 1mg/kg every third day for 2 weeks then to be stopped if possible. |

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| | • Intravenous steroid therapy was initiated for 2-3 days in nine of the dogs without reason given for this.<br>• Where possible a CBC was performed at 7 days after each CA treatment. |
| **Study design:** | Retrospective case series |
| **Outcome studied:** | Response to prednisolone and subcutaneous CA treatment in dogs with MUO.<br><br>Subjective<br>• Quality of life was judged by the owner and referring veterinarian.<br>Objective:<br>• Survival time and cumulative probability of survival at 2 years. |
| **Main findings: (relevant to PICO question):** | • At the end of the study seven dogs were alive and four had died (one due to drowning, one due to neurologically associated pancreatitis and hypoglycaemia, one dog euthanised at the first relapse and the other dog euthanised at the fourth relapse).<br>• Median survival 384 days, range 78-603.<br>• Median survival time could not be calculated using Kaplan-Meier analysis as fewer than half the animals had died. The cumulative probability of survival at 2 years was 58.4%.<br>• Initial response to treatment was judged as excellent with total remission of clinical signs and excellent quality of life in five dogs, good with partial remission and good quality of life in five dogs, and poor with poor control of disease in one dog.<br>• Seven dogs experienced relapses. In three of these relapse occurred due to steroid dose reduction. In one of these dogs another relapse occurred due to a delay in CA treatment due to pyometra. One dog had a relapse with discontinuation of its CA treatment by the owners. In three cases the cause of relapse was unknown. One of the dogs who relapsed after 3 months of treatment was euthanised as the owner would not accept further treatment. |
| **Limitations:** | • No standard treatment protocol, tapering dose altered by clinicians depending on each dog's response to treatment, side effects, number of relapses and owner compliance.<br>• Varied CA treatment cycles ranging from 4 to 37 treatments.<br>• Only one dog had clinical confirmation of GME.<br>• Only included cases that survived long enough for CA therapy.<br>• Small number of cases collected for the study.<br>• No mention of survival in text only in table form.<br>• No account for 3/7 cases of relapse.<br>• Subjective quality of life assessment. |

| **Zarfoss** (2006) | |
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| **Population:** | Dogs presenting to the Cornell University Hospital for Animals with MUO |
| **Sample size:** | 10 |
| **Intervention details:** | • Dogs were selected based on treatment with a combination of steroids and CA.<br>• Covered some of the six criteria for MUO presumptive diagnosis including focal or multifocal CNS signs, negative PCR and CSF analysis for infectious disease (five dogs), CSF protein and WBC analysis (CSF mononuclear pleocytosis), CT signs consistent with MUO (nine dogs), ophthalmoscopy signs of optic neuritis, histopathological diagnosis.<br>• A minimum database of CBC, serum biochemistry profie, blood serology for infectious encephalopathies (*Anaplasma phagocytophilum*, *Ehrlichia canis*, *Toxoplasma gondii*, *Neospora canis, Cryptococcus* (in nine dogs). Antinuclear antibody titres were performed in two dogs with immune-mediated disease.<br>• Each dog was treated with immunosuppressive doses of corticosteroids. Six dogs received 0.1-1.0mg/kg oral dexamethasone sodium phosphate or 10-30mg/kg methylp sodium succinate. All dogs received 1-2mg/kg prednisolone twice daily at the time of diagnosis.<br>• Approximately 15mg/kg Clindamycin was given twice daily and 5mg/kg Doxycycline twice daily were given initially but discontinued after negative infectious disease titres (5-7 days after diagnosis).<br>• CA treatment was initiated at variable intervals (from 0 to 60 days later) at 50mg/m$^2$ subcutaneously twice a day for two consecutive days. The CA protocol was repeated every 3 weeks for 4 months (where the treatment interval was then lengthened by a week every 4 months with a maximum final interval of every 8 weeks).<br>• One dog had repeat CT at 7 months and two dogs (including the dog with repeat CT) had repeat CSF analysis. |
| **Study design:** | Retrospective case series |
| **Outcome studied:** | Whether prednisolone with subcutaneous CA is safe for use in canine MUO.<br><br>Subjective:<br>• Clinical response to therapy through follow-up appointments, telephone follow-ups with owners or referring vets.<br>Objective:<br>• Survival time |

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| **Main findings: (relevant to PICO question):** | • Partial (over 50% reduction of clinical signs) or complete remission was achieved in all dogs receiving corticosteroid and CA treatment.<br>• Median survival for all dogs was 531 days (Kaplin-Meier product limit method). Survival ranged from 564 to 1025 days at the time of writing.<br>• The dog with survival time of 46 days was the only dog in which post-mortem histopathology was available disclosing NLE and excluded from survival range data.<br>• Two dogs required tertiary immunosuppressive chemotherapy of procarbazine or leflunomide.<br>• One dog received azathioprine for a history of immune-mediated haemolytic anemia (IMHA) until CA treatment was established.<br>• Two dogs received phenobarbitol and/or potassium bromide for persistent episodic seizures.<br>• In one dog, at attempts to increase CA treatment interval the dog relapsed neurologically.<br>• Dogs starting CA treatment earlier did not have longer survival times compared to those started at 60 days after prednisolone therapy. |
| **Limitations:** | • No standard treatment protocol, differing dose ranges and CA administered at different time periods after diagnosis.<br>• Diagnosis and exclusion of a case of NLE post-mortem but no other definitive diagnostic information for other cases.<br>• Small number of cases collected for the study.<br>• Only included cases that survived long enough for CA therapy.<br>• One dog had a positive CSF culture with no information of repeat to rule out positive infection, even if contamination suspected.<br>• Three dogs had a history of immune-mediated disease; keratoconjunctivitis sicca and generalised vaccine reaction, IMHA and juvenile Addison's disease. |

## Appraisal, application and reflection

All cases of MUO were assumed through neurological examination and included some or all of advanced imaging techniques, CSF analysis or diagnosed with antemortem brain biopsy or postmortem histopathology. It should be taken into account that each of these studies is focused on populations of animals attending referral centers rather than general practice. None of the studies directly compared the treatment of MUO with either a combination therapy of CA with prednisolone to prednisolone as a sole therapy. Only one study evaluated the use of prednisolone as a sole therapy for treatment of MUO, but was used as a comparison for a different chemotherapeutic agent and involved a range of different treatment doses, including at the initiation of therapy. Three out of six studies were performed by a retrospective search of cases. This may lead to selection bias and may not give accurate representation evaluating treatment of MUO as some cases may die shortly after admission or prior to commencing treatment (e.g. Lowrie et al., 2016). Retrospective case series sit low on the hierarchy of evidence and despite some of the studies having greater strength (randomised controlled trial > cohort study > case series), it is difficult to draw definitive conclusions from the available literature.

A treatment protocol was implemented in three of the studies, however the prednisolone dose or frequency in these, as well as the studies without a treatment protocol, would be altered to the individual patients based upon relapses and clinical signs. Of the five studies receiving CA, three received SC CA (not including Lowrie et al., (2016) historical control group), one a single IV dose of CA, and one IV CA followed by SC CA. Lowrie et al (2016) found significantly better survival with dogs receiving their first dose of CA by CRI followed by SC compared with dogs receiving only SC CA. Smith et al (2009) also noted an increase in estimated mean survival when compared with other studies (median survival estimate 1063 days). Almost all dogs treated with CA and prednisolone surviving to 3 months went on to survive to 12 months (Lowrie et al., 2016; Lowrie et al., 2013; Smith et al., 2009).

It is not possible to directly compare CA with prednisolone to prednisolone as a sole therapy for treatment of MUO from the available literature. When comparing actual or estimated survival between the studies, CA with prednisolone has greater median survival time in all studies compared to prednisolone as a sole therapy. It should be noted that in Lowrie et al (2013), 13/39 dogs died within 3 days of diagnosis regardless of treatment regime. In order to better evaluate the effect of CA with prednisolone as a treatment option a prospective randomised clinical trial using a standardised treatment protocol is required.

This review highlights the matter that limited studies have been performed investigating the use of combination therapy of CA and prednisolone in MUO.

## Methodology Section

| **Search Strategy** | |
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| Databases searched and dates covered: | The search was applied to CAB abstracts and Medline databases from 1946 to January 2017. |
| Search terms: | Canine OR dog OR dogs OR dog diseases AND meningoencephalitis OR granulomatous meningioencephalitis OR meningioencephalomyelitis OR MUO OR GME OR MUE OR NLE OR NME OR reticulosis AND cytarabine OR cystosine arabinoside OR cytosine arabinoside OR prednisolone OR prednisone. |
| Dates searches performed: | Monday 2nd January 2017 |

| **Exclusion / Inclusion Criteria** | |
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| Exclusion: | Single-case reports, duplicate papers, articles in which cytarabine with prednsiolone or prednisolone as a sole therapy for treatment of MUO was not evaluated, or articles where the full text was not available in English or able to be located. |
| Inclusion: | Articles published between 1946 and present investigating the effect of cytarabine in combination with prednisolone or prednisolone as a sole therapy for treatment of mengioencephalitis of unknown origin. |

**Search Outcome**

| Database | Number of results | Excluded – single case report | Excluded – not relevant to the PICO | Excluded – not available in the English Language | Total relevant papers |
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| CAB Abstracts | 40 | 16 | 17 | 1 | 6 |

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| Medline | 29 | 11 | 11 | 1 | 6 |
| Total relevant papers when duplicates removed | | | | | 6 |

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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