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Treatment Duration With Steroid Monotherapy in Dogs With Steroid Responsive Meningitis-Arteritis

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

In dogs suspected of having steroid responsive meningitis-arteritis (SRMA), how long should immunosuppressive monotherapy with steroids be undertaken in order to achieve clinical resolution without relapse of clinical signs?

Clinical bottom line

Based on the currently available literature, steroid treatment using the protocol outlined in Lowrie et al. (2009) at a gradually tapering dose over a course of 6 months, appeared to lead to clinical remission in all cases, with a disease free post treatment interval of at least 6 months. However, further research is needed as there are currently three published papers with a low number of cases, so a definitive time course cannot be suggested until stronger evidence is available.

Clinical Scenario

You are presented with an 18-month-old female neutered Beagle with a history of anorexia and lethargy. On examination the dog shows cervical hyperesthesia and has a rectal temperature of 39.8°C. Cerebral spinal fluid (CSF) analysis reveals a marked neutrophilic pleocytosis with elevated protein. A presumptive diagnosis of steroid responsive meningitis-arteritis (SRMA) is made, and you wish to start the dog on immunosuppressive monotherapy with steroids, however you are unsure as to how long the dog will require treatment to achieve clinical resolution and without relapse of clinical signs.

Summary of the evidence

Tipold & Jaggy (1994)	
Population:	Dogs with clinically confirmed SRMA referred to the Institute of Animal Neurology, University of Berne, Brem-gartenstrasse, Switzerland during an unspecified time frame
Sample size:	20 dogs
Intervention details:	- All cases were diagnosed based on clinical and neurological examination, Complete Blood Count (CBC) and serum biochemistry and CSF analysis. Some dogs had additional testing including electromyography (EMG), electroencephalography (EEG), myelography , Computed Tomography (CT) and cisternography - Dogs received prednisolone at 4 mg/kg/day. This was reduced to 2 mg/kg/day after 2 days and maintained for 2 weeks, followed by 1 mg/kg/day for a further 2 weeks - At this point dogs returned for examination to include CSF

	analysis, blood profile and EEG. These were repeated every month since the beginning of the treatment for at least 6 months - As soon as neurological exam and CSF analysis were normal, the prednisolone dose was reduced from 1 mg/kg/day until 0.5 mg/kg every other day was achieved for 6 months. The treatment was stopped when dogs presented clinically normal with normal CSF and blood profile - When pleocytosis was still detected, the same dosage was maintained for 6 months
Study design:	Prospective single centre case series
Outcome studied:	The diagnostic usefulness of ancillary testing and response to a treatment protocol Subjective: - Follow-up of dogs for up to 4 years after cessation of treatment protocol Objective: - Occurrence of abnormalities in CSF analysis, blood profile and EEG at monthly follow-ups
Main findings: (relevant to PICO question):	- 12/20 dogs that entered the study had no clinical signs following the described treatment regimen and were free of neurological signs for up to 4 years after treatment was stopped - 2/20 improved but were still under treatment at the time of the article's publication - 3/20 cases relapsed after stopping the 6 month treatment schedule - One dog was euthanised - The outcome was unknown in the two others
Limitations:	- Cases are from a single referral hospital; this population may not be directly comparable with other populations i.e. those seen in first opinion practice - Small population size - The study is 23-years-old - There is minimal to no statistical analysis - No details on how 4 year follow-up was obtained

Cizinauskas, Jaggy & Tipold (2000)	
Population:	Dogs with clinically confirmed SRMA referred to the Small Animal Neurology Department, University of Bern, between March 1995 – May 1997
Sample size:	9 dogs
Intervention details:	- All cases were diagnosed based on clinical and neurological

	examination, Complete Blood Count (CBC) and serum biochemistry and Cerebral Spinal Fluid (CSF) analysis. Some dogs had additional MRI and infectious disease PCR testing. - All dogs were treated with a standard protocol initiated with oral prednisolone at 4 mg/kg/day. After 2 days this was reduced to 2 mg/kg/day orally for 2 weeks, followed by 1 mg/kg/day orally for 1 month. Dogs were rechecked at one to three month intervals which included clinical examination, complete blood count and biochemistry, and CSF tap - Once results of neurological and CSF examination were found to be in normal range, prednisolone dose was reduced to half the previous dosage until 0.5 mg/kg every alternate day was reached - If pleocytosis was present in CSF, initial dosage was maintained. This therapeutic regimen was maintained for at least 4 months until there were no clinical signs of SRMA and CSF tap and blood results were normal in the two latest follow-up examinations - In dogs that relapsed, the prednisolone dose they were on at the time was doubled. Dogs with frequent and severe relapses, which did not respond to routine treatment (prednisolone 1 mg/kg/day), received additional immunosuppressive therapy with mycophenolate mofetil at 20 mg/kg every other day, alternating with prednisolone (0.5 or 1 mg/kg). Prednisolone was continuously reduced down to 0.5 mg/kg every third day, then once a week and later withdrawn if clinically improving - Two dogs were treated initially with meloxicam 0.1 mg/kg once daily. One dog was put on prednisolone treatment after relapsing, while the other was treated with meloxicam only
Study design:	Retrospective single centre case series
Outcome studied:	Response to treatment and side effects of long-term glucocorticoid steroid therapy Subjective: - Long term follow-up of 8–34 months; for 7 dogs this was longer than 18 months - Final examination 2–8 months after treatment terminated, regularly contacted thereafter via telephone Objective: - CBC, biochemistry and CSF analysis at 1–3month intervals - Relapse of cases demonstrated by recurrence of clinical signs and abnormal CSF analysis - Results of clinical examination and CSF analysis at follow-up at 18 months
Main findings: (relevant to PICO question):	- Side effects included poly uria and poly dipsia (n=7), polyphagia (n=6), urinary tract infection (n=3), hyperpigmentation, alopecia, Gastrointestinal signs and

	hepatomegaly (n=2) - 8/9 dogs were free of neurological signs up to 29 months after termination of treatment - 4/9 dogs were disease free throughout the follow up period • Three dogs on steroids alone finished treatment at 4, 7, and 9 months after diagnosis without relapse. These were observed for 28, 26 and 8 months respectively, and were relapse free. • One dog on meloxicam alone finished treatment 2 months after diagnosis without relapse. It was observed for 11 months and was relapse free - 4/9 had relapses of SRMA • These four dogs had frequent and severe relapses after diagnosis and required additional immunosuppressive therapy with mycophenolate mofetil as well as steroids at 5, 7, 9 and 13 months • Of these four dogs, one dog stopped all treatment 13 months after diagnosis, one dogs' follow up period ended at 12 months whilst on steroids and mycophenolate mofetil, one dog stopped all treatment 20 months after diagnosis and one dog stopped taking steroids and mycophenolate mofetil at 19 months and 27 months after diagnosis respectively • Case 9, 5, 7 and 10 were observed for 11, 0, 5 and 4 months respectively and showed no signs of relapse in this period - One dog was euthanised at 8 months following relapse on steroids alone, at the owners' request
Limitations:	- Retrospective study - Cases are from a single referral hospital; this population may not be directly comparable with other populations i.e. those seen in first opinion practice - Small population size - Four dogs were treated with steroids prior to study - Abstract identifies ten dogs, however only nine in study and eight available for follow-up. One dog is missing from the follow-up and not accounted for. The discrepancy in numbers is not explained - The study is 18-years-old - There is minimal statistical analysis - No standard treatment protocol between animals - No standardised duration of observation period

Lowrie et al. (2009)

Population:	Client owned dogs with clinically confirmed SRMA presenting to the small animal neurology service at University of Glasgow Small Animal Hospital (UGSAH) between May 2006 – May 2008
Sample size:	20 dogs
Intervention details:	- All dogs received a physical examination, complete blood count, biochemistry, orthogonal cervical radiographs and CSF analysis of cytology and total protein concentrations - Dogs with neurological deficits underwent Polymerase Chain Reaction (PCR) for infectious diseases and Magnetic Resonance Imaging (MRI) to rule out other disease - All dogs were treated with a standard protocol initiated with oral prednisolone at 2 mg/kg q. 12 hours for 2 days, then 1 mg/kg q. 12 hours for 12 days - If remission was achieved, prednisolone was continued at 0.5 mg/kg orally q. 12 hours for 6 weeks, then reduced to 0.5 mg/kg orally q. 24 hours for 6 weeks, then reduced to 0.5 mg/kg orally q. 48 hours for 6 weeks, then reduced to 0.5 mg/kg orally every third day for 6 weeks before stopping, and resolution considered - If a putative relapse was considered, the protocol was restarted with prednisolone at 1 mg/kg orally q. 12 hours for 2 weeks - A recheck examination was scheduled 2 weeks after starting treatment and involved a clinical examination and CSF analysis - Remission was defined as absence of clinical signs in addition to normal CSF analysis - A failure to achieve clinical remission at recheck involved following the above protocol with a further second recheck 2 weeks later - Failure of the protocol was defined as two consecutive cycles without achieving clinical remission - Once clinical remission was achieved, no further CSF samples were obtained unless relapse suspected - At presentation, remission, and putative relapse, a history, general and neurological examination, Complete Blood Count (CBC), serum biochemistry and Acute Phase Protein (APP) panel were obtained - Serum samples were taken at resolution, defined as 4 weeks after cessation of therapy without the recurrence of clinical signs - The minimum follow-up for each case was 6 months after cessation of prednisolone
Study design:	Prospective single centre case series
Outcome studied:	Response to therapy, long term outcome and expression of potential disease markers of SRMA as potential diagnostic indicators Objective: - CBC, biochemistry and CSF analysis at presentation,

	remission (2 weeks into treatment) and resolution (4 weeks after cessation of treatment)
Main findings: (relevant to PICO question):	- All 20 dogs responded to the 6 month course of prednisolone therapy - Four out of 20 dogs were suspected of suffering putative relapses with 1 dog having two separate episodes All four dogs suspected of relapsing remained on treatment protocol and increased prednisolone dose as described, resulted in resolution of clinical signs with a 6 month follow-up period - Prednisolone monotherapy was successful in achieving full remission in 20/20 affected dogs, with an in protocol relapse rate of 20% (4/20 dogs) - Suggests relapse has a propensity to occur on treatment and not after cessation of treatment - The described therapy resulted in disease free post treatment interval of at least 6 months
Limitations:	- Small population size - Cases are from a single referral centre; this population may not be directly comparable with other populations i.e. those seen in first opinion practice

Appraisal, application and reflection

The available evidence was split between a retrospective case series and two prospective case series. A retrospective case series is low on the hierarchy of evidence and therefore taking a meaningful conclusion clinically from its results is difficult. Case series studies also have a high likelihood of bias.

All papers suffered from a small sample size and are focused on a population of animals attending a referral centre rather than general practice.

There was standardisation across all papers regarding diagnosis of SRMA; all cases were diagnosed based on clinical and neurological examination, CBC and serum biochemistry as well as CSF analysis. Select cases underwent further ancillary testing such as EEG and EMG (Tipold & Jaggy, 1994), and MRI and infectious disease PCR (Lowrie et al., 2009).

There were confounding variables in Cizinauskas et al. (2000); four dogs were pre-treated with steroids prior to inclusion in the study, there was no defined follow-up period for these cases, and only three dogs received steroid monotherapy. Pretreatment with steroids was an exclusion criterion of Lowrie et al. (2009). A standardised treatment protocol for both relapses and follow-up were defined in Lowrie et al. (2009), however Tipold & Jaggy (1994) did not detail a treatment protocol for relapse.

It appears from the available literature that a 6 month tapering steroid monotherapy protocol as per Lowrie et al. (2009) is effective at controlling clinically confirmed SRMA and resulted in a 6-month disease free post-treatment interval. A similar standardised 6 month treatment protocol was suggested by Tipold & Jaggy (1994) which described a 4 year disease free period post-treatment, however details of how follow-up data was obtained is lacking.

It is difficult to draw meaningful conclusions from Cizinauskas et al. (2000) due to the retrospective nature, small sample size and confounding variables. Both prospective studies were based on a small sample size from a referral population, and Tipold & Jaggy (1994) is a 23-year-old paper.

The available evidence, however, is limited and would benefit from studies of a higher power i.e. prospective, randomised, blinded studies, before a definitive recommendation of treatment duration can be made.

Methodology Section

Search Strategy	
Databases searched, and dates covered:	The search was applied to CAB abstracts via the Ovid platform, covering 1973 to 2018 week 40 Medline via the Ovid platform from 1946 to 2018
Search terms:	((dog or dogs or canine* or canid* or bitch*) AND (steroid responsive meningitis-arteritis or steroid responsive meningitis arteritis or SRMA))
Dates searches performed:	Friday 11 October 2018

Exclusion / Inclusion Criteria	
Exclusion:	Single case reports, duplicate papers, book chapters, conference proceedings, articles where the full text was not available in English or able to be located, or articles not relevant to the PICO question.
Inclusion:	Articles published between 1946 – present, articles in English and relevant to the PICO, articles with more than one animal, articles that used steroids as the only immunosuppressive.

Search Outcome

Database	Number of results	Excluded – not relevant to the PICO	Excluded – single case report/book chapter/conference proceeding	Excluded – Not available in English	Total relevant papers
CAB Abstracts	74	51	16	4	3
Medline	53	44	6	0	3
Total relevant papers when duplicates removed					**3**

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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