Inflammatory diseases of the CNS can affect the brain, meninges and/or the spinal cord. Most disease processes causing meningitis also cause an associated encephalitis and or myelitis in animals. Non infectious and presumed immune mediated forms of meningoencephalomyelitis are much more common in dogs than infectious causes. In most immune mediated conditions the cause of the immune system abnormality is not established. Presumed immune mediated diseases include corticosteroid responsive meningoencephalomyelitis, granulomatous meningoencephalomyelitis (GME), necrotising vasculitis, breed specific necrotising meningoencephalitis (pug dog, maltese, chihuahua) and necrotising leucoencephalitis (yorkshire terrier). A definitive diagnosis is made on histopathology and in most cases an ante mortem diagnosis cannot be made as clinical signs and results of diagnostic tests are often very similar – and also may be indistinguishable from infectious causes of meningoencephalomyelitis, vascular diseases and some neoplastic diseases of the CNS without histopathology. These histopathologic distinctions in non inflammatory meningoencephalitis may or may not represent different underlying causes (or immune mechanisms).

Corticosteroid responsive meningitis (CSRM, polyarteritis, necrotising vasculitis, beagle pain syndrome))

CSRM is seen predominantly in young large breed dogs (average age 1 year) although can occur in smaller breeds (eg polyarteritis of Beagles - also called Beagle pain syndrome, Nova Scotian duck tolling retrievers and more recently Italian greyhounds). Presenting signs are indicative of meningitis with spinal pain, abnormal posture, stiff gait, dullness and lethargy. Pyrexia is common and CBC may show leucocytosis. Clinical signs may be acute and severe or may be episodic. Neurologic deficits (paresis/paralysis) are uncommon but may reflect spinal cord or occasionally brain involvement). A necrotising vasculitis of spinal leptomeningeal vessels has been described in young Beagles, GSHPs and Bernese mountain dogs and may occur occasionally in other dogs. Clinical signs are as for CSRM however signs of multifocal or focal spinal cord disease may be seen. Treatment is as for CSRM but prognosis depends on degree of spinal cord damage.

CSF analysis typically shows marked pleocytosis with neutrophil counts as high as >10,000/uL. CSF analysis may be normal between episodes. Infectious agents are not seen in the CSF and CSF culture is negative. Some animals may have concurrent polyarthritis. Treatment is with long term corticosteroids initially 2-4mg/kg/day and tapered over 3-6 months. Prognosis is good in animals with meningitic signs only however relapses are common. Azothiaprine may also be used to treat affected dogs if corticosteroids are not effective alone or side effects are tolerated poorly.
responsive meningitis is also seen occasionally in cats. A predominantly eosinophilic pleocytosis can be seen in some affected dogs (eosinophilic meningitis) however the most common cause of eosinophilic pleocytosis in east coastal Australia is parasitic meningoencephalomyelitis associated with infection with angiostrongylus cantonensis larvae (rat lungworm).

The term GME has often been used to include all of the other noninfectious CNS inflammatory diseases (excluding CSRM) although the pathology may not be the same in all cases. The terms meningoencephalitis (or meningoencephalomyelitis) of unknown aetiology or origin(MUA or MUO or MUE if American) has been proposed as a more accurate diagnosis. Other proposed or previously used descriptions include non pathogenic meningoencephalomyelitis , non infectious inflammatory CNS disease, non suppurative meningoencephalitis , reticulosis etc. For the current purpose the term GME (rightly or wrongly) will be used to describe all non infectious inflammatory CNS disease as it is a widely recognized term. It has a worldwide distribution and may account for up to 25% of ALL CNS disorders in dogs.

GME is recognised most commonly in toy and small breed dogs especially Maltese, miniature poodles and terriers of all kinds (including Staffordshire terriers and Airedales). It can however occur in all breeds including large breeds and crossbred dogs. It is seen most commonly in middle aged dogs (less commonly in dogs <2 years and >10 years). Both sexes affected although females may outnumber males.

The diagnosis of non infectious CNS inflammatory disease is made on the basis clinical findings and the exclusion of infectious causes -often based on serology, CSF analysis, and brain imaging. In many cases however a tentative diagnosis is made based on best guess considering breed, age, history and clinical signs. Typically animals with CNS inflammatory disease present with an acute onset of multifocal CNS signs (brain or spinal cord) and/or hyperesthesia (cervical or thoracolumbar). Clinical signs include forebrain abnormalities (alterations in mentation, compulsive circling, seizures), and/or caudal fossa abnormalities (ataxia, vestibular disturbance, cranial nerve abnormalities) and/or spinal cord disease (any level). In many cases it is difficult to make a neuroanatomic diagnosis. However, a more chronic progressive history and in some cases an episodic history is seen and a significant number of dogs present with focal neurologic signs. Animals with meningitis often have severe neck pain, hunched posture and show reluctance to move and a stiff stilted gait. Many small dogs have a history of hiding and yelping or screaming when picked up for no apparent reason. Poorly localisable spinal pain is common. Not all affected dogs however will show evidence of spinal pain.

Focal spinal cord signs (of any part of the spinal cord but especially cervical) including paresis or paralysis may be seen. An optic neuritis form of GME is often described but is uncommon. Clinical signs can be acute in onset and rapidly progressive or more insidious in onset and slowly progressive over weeks or months. In summary GME can present with any history, any neurologic signs, at any age in any breed!

Attempts to characterise forms of GME as disseminated, focal or optic have been made. This is often difficult antemortem and may not be significant with respect to diagnosis, treatment and prognosis.

The breed specific necrotising meningoencephalitides (pug dog, maltese, chihuahua and yorkshire terrier) may present at an earlier age (<1 year especially maltese and pugs) but may also be seen in older dogs (especially Chihuahuas). Typically these
encephalitides present with an acute onset of severe forebrain disease including seizures. Neurologic abnormalities are often rapidly progressive. Again these diseases have been characterized in different breeds depending on whether there is meningeal involvement, predominantly white matter involvement and location (cerebral hemispheres or brainstem or both). These may represent different disease processes but may represent different probably genetically determined immune responses.

Generally there are no abnormalities on physical examination or on haematology or biochemistry profile in affected dogs with any form of non infectious inflammatory CNS disease. Pyrexia may be seen but is uncommon. **CSF analysis** generally shows mild to moderate pleocytosis with a predominance of mononuclear cells and variable increases in CSF protein. Total WBC count can vary from <10 cells to > 5,000 cells. CSF protein may be normal or up to 4g/L. Neutrophils usually account for less than 50% of cells seen. Macrophages and occasional eosinophils may also be seen. Some dogs (may be more than 10%) will have a normal CSF. CSF findings may indicate inflammation that is suggestive of GME but other conditions can also cause a similar CSF picture including infectious causes, vascular disease (infarct) and neoplasia. In most cases CSF analysis does not provide a definitive diagnosis but can be one of the pieces of a puzzle when trying to establish a likely diagnosis in cases of spinal or intracranial disease. CSF analysis will determine whether inflammation is present but only if inflammation involves the meninges, ependymal lining or tissue close to CSF pathways. Non specific CSF abnormalities are commonly seen in vascular, traumatic, degenerative, neoplastic and inflammatory CNS conditions.

**Significant risk is associated with the collection of CSF** in animals with increased intracranial pressure (ICP) where brain herniation, either of the cerebral hemisphere/s under the tentorium cerebelli or herniation of the cerebellum through the foramen magnum, is a possible sequela. CSF collection is also risky in animals with severe brain disease with or without increased intracranial pressure where changes in cerebral perfusion associated with anaesthesia and lack of normal brain autoregulatory responses may result in further deterioration in neurologic status. **Unfortunately these are often the animals where CSF analysis is of most value.** Clinical signs associated with increased ICP include obtundation, stupor, panting, headpressing, bradycardia and increased systemic blood pressure. Some animals with increased intracranial pressure will not have any obvious clinical signs.

**Damage to neural structures (spinal cord or medulla oblongata) is also a risk with cisternal CSF collection,** especially in small animals or in animals with obstruction to CSF flow at the level of the cerebellomedullary cistern. The majority of dogs with GME are small and may be of breeds with cranio- cervical junction abnormalities such as Chiari like malformation. I do not routinely perform CSF collection in dogs with a high index of suspicion of GME especially those with neurologic abnormalities indicative of brain disease. **CSF analysis is useful in the assessment of animals with spinal cord or meningeal disease** (in my hands usually by lumbar collection).

**Brain imaging may also show abnormalities suggestive of inflammatory disease** and MRI is the diagnostic modality of choice in GME. Magnetic Resonance imaging (MRI) is the most sensitive imaging technique in evaluating the brain and spinal cord. Higher strength magnets 1.0T, 1.5T allow better imaging of inflammatory lesions than low strength magnet MRI. There is however no “typical” MRI picture and lesions may be indistinguishable from infectious, vascular or neoplastic disease. Single or multiple
lesions may be seen anywhere in the neuroaxis that may be hypointense on T1 weighted images, and hyperintense on T2 weighted and FLAIR images. Contrast enhancement is variable. Meningeal enhancement may be evident. Multifocal lesions however are most typical. Imaging is useful also in ruling in or out other causes of intracranial or spinal cord disease including neoplasia and vascular lesions however focal GME granulomas may have a very similar appearance to neoplasms and infarctive lesions due to inflammation may appear very like vascular lesions due to other causes. The lesions of necrotizing encephalilitis in chihuahuas, pugs, maltese etc are characteristic of this disease with loss of normal grey and white matter demarcation multifocally within the cerebral hemispheres with areas of hyperintensity on T2 and hypointensity on T1 corresponding to areas of necrosis.

In some cases of inflammatory CNS disease no abnormalities are seen on MRI. Computed Tomography (CT) is less sensitive especially in evaluating caudal fossa lesions (beam hardening artifact). “Mass effect” – deviation of the falx or disruption of normal brain anatomy may or may not be seen in either CT or MRI. A definitive diagnosis of GME can only be made on histopathology which can be achieved by brain biopsy or brain examination which is obviously difficult ante mortem! Microscopically GME is characterized by perivascular lymphocytic and/or macrophage cuffing. These lesions may coalesce into macroscopic granulomas.

**A tentative diagnosis of GME** is often made by exclusion of other causes (serology/culture of CSF in some circumstances) and in many cases on response to treatment. To rule out infectious causes of meningoecephalitis serum Cryptococcal antigen titre (LCAT), serum toxoplasma gondii and neospora caninum antibody titres (and in some instances CSF titres) may be necessary. CSF culture is often negative even in cases of bacterial or fungal infection.

**In animals with severe neurologic signs the benefits of diagnostic tests especially CSF analysis need to be weighed against the risks of the procedure.**

The cause of GME is not known- autoimmunity is most likely and GME may represent a T cell mediated hypersensitivity.

**The prognosis is difficult to predict.** GME can be an acute, rapidly progressive and fatal disease despite treatment but many cases of presumed GME have responded well to treatment and remained in remission for months to years. Most literature on GME gives a poor to hopeless prognosis associated with this disease but in practice many apparent GME cases do well. It is a histologic diagnosis and the literature is largely based on animals with a confirmed diagnosis (ie are dead). **Prognosis cannot be based on the severity of clinical signs on presentation nor on the degree of abnormality on CSF analysis or brain imaging.**

**Immunosuppressive doses of corticosteroids (primarily prednisolone)** remain the mainstay of treatment. **In many cases (for financial and/or risk of further diagnostic testing) empiric treatment is indicated without a more definitive diagnosis.** Starting dose of prednisolone is 1-2mg/kg q12 hours. Small dogs (<10kg) should be given 2mg/kg q12 hours. Dogs <2.5 kg should be treated as a 2.5 kg dog and those <5kg as a 5kg dog. Larger dogs (>40kg) should be treated as a 40kg dog and I would generally give no more than 40mg q12 hours for extended periods of time. Affected dogs may take several days to show any response to corticosteroid therapy. The dose of prednisolone is tapered over at least 6 months depending on clinical response. Initially the dose should be reduced after 2-4 weeks. If remission is achieved
animals should be maintained on prednisolone (0.5-1mg/kg every other day or 2-3x a week) for 1-2 years or life. Whether affected animals are “cured” is difficult to determine. If a dog is free of neurologic signs for > 6 months and managed with prednisolone at a low dose 2-3 x a week treatment may be discontinued. However corticosteroid side effects especially in larger breed dogs are a significant problem in the long term. Long term high dose corticosteroids cause iatrogenic hyperadrenocorticism with significant muscle wasting and calcinosis cutis. Treatment also predisposes to gastrointestinal ulceration, pancreatitis, diabetes mellitus, infection (especially UTI) ligamentous and tendon injury. Small dogs often tolerate high dose therapy well, however in dogs which show a recurrence of neurologic signs with corticosteroid therapy or require high levels of corticosteroids (> 1mg/kg) for long periods to alleviate neurologic signs or have significant corticosteroid side effects other immunosuppressive drugs should be considered. In larger breed dogs adjunctive therapy with other drugs should be considered early as high dose corticosteroid treatment is often poorly tolerated. In all dogs with significant neurologic deficits associated with spinal cord involvement additional therapy eg cytarabine should be considered early. The use of other immunosuppressive drugs may enable a reduction in the dose of prednisolone given, however for most animals treatment with some level of prednisolone is also necessary.

**Azathioprine (Imuran)** is immunosuppressive and acts to inhibit T cell function. It does not cross the blood brain barrier in normal dogs. Although it may be useful in the treatment of corticosteroid responsive meningitis especially in young large breed dogs, in my hands it does not seem to be helpful in dogs with GME. Having said this, other clinicians have recommended treating with imuran and have had some success using azothiaprine in combination with prednisolone allowing for a reduction in prednisolone dose. It is relatively free of side effects with myelosuppression the main concern at higher doses. Recommended dose is 0.5-1.0mg/kg q48 hours. 2mg/kg q24 hours for first 5-7 days may be used.

**Cytosine Arabinoside (Cytarabine, Ara-C)** is a drug that has been used as an antineoplastic agent in dogs and humans and has been used to treat CNS lymphoma. Its mechanism of action is not known. Due to its ability to cross the blood brain barrier and its immunosuppressive effects cytarabine was proposed as a potential treatment for GME approximately 6 years ago. Most authors recommend treatment with 50mg/m2 by subcutaneous injection twice a day for 2 consecutive days with this cycle repeated every 3 weeks. This dose is lower than doses generally used as part of chemotherapeutic protocols for neoplasia. Side effects associated with Cytarabine are few. Myelosuppression (seen generally 10-14 days post initial treatment) is reported but is generally not a clinical problem. CBC should be monitored periodically but is not necessary at every cycle. Vomiting, diarrhea and/or inappetance may occur after treatment. Cytarabine is inexpensive (when purchased in 10ml vials) and animals can be treated on an outpatient basis however gloves should be worn when administering this drug and handling/disposing of urine and faeces. Cytarabine is used in conjunction with prednisolone and I usually reduce the prednisolone dose incrementally after each 2 cycles of cytarabine if an animals neurologic status is stable. Cytarabine can be used indefinitely.

**Leflunomide (Arava)** is an immunomodulatory drug used in humans primarily in the treatment of rheumatoid arthritis. It has been used in dogs in conjunction initially with corticosteroids and as “stand alone” agent in dogs with unmanageable corticosteroid side effects with reported success. The dose given is 2mg/kg once a day initially. In my
hands treated animals have relapsed or not improved. It is not associated with any significant side effects and is given orally. It can also be given with prednisolone.

**Cyclosporin** has also been proposed as a treatment for GME as it has been suggested that GME is a T-cell mediated autoimmune disease. Cyclosporin is a potent immunosuppressive drug and suppresses T-cell mediated immune responses. The blood brain permeability of cyclosporine however is poor in normal animals. However GME is a perivascular disease and the blood brain barrier is likely to be disrupted and it is proposed that cyclosporin concentration is probably higher in affected areas of the CNS. I have limited experience with this drug and it has not been helpful in treated dogs (2) that have failed on treatment with prednisolone and cytarabine.

**Procarbazine** is an antineoplastic drug that is lipid soluble and readily crosses the blood brain barrier and used predominantly in human medicine to treat lymphoma. A dose of 25-50 mg/m2/day has been recommended. Procarbazine is associated with a high incidence of side effects including myelosuppression (30%), haemorrhagic gastroenteritis (15%), nausea, vomiting and hepatic dysfunction. I have no experience with this drug and its efficacy has not been proven. Its side effects and availability limit its use.

**Lomustine (CCNU)** is an antineoplastic alkylating agent in the nitrosurea class that is highly lipid soluble and crosses the blood brain barrier. The dose used to treat GME is relatively arbitrary but high doses are not recommended. Treatment with lomustine is associated with significant and in some cases life threatening myelosuppression, gastrointestinal ulceration and hepatotoxicosis. Side effects increase with increased dose but may also be seen after an initial, relatively low dose. Sepsis is a significant risk with myelosuppression. Toxicity is not predictable and I have not recommended its use routinely as a first choice treatment.

**Animals with seizures should also be treated with an anticonvulsant.** Affected animals should not be vaccinated unless absolutely necessary. Relapse of clinical signs may be seen after vaccination. A low fat diet is also recommended.

**Response to therapy** is generally assessed on improvement or resolution of clinical signs. Repeating CSF analysis is not generally recommended as the degree of abnormality (or lack thereof) on CSF analysis has not correlated well with the severity of CNS inflammation.

In my experience at least 60% of dogs with presumed GME or non infectious corticosteroid responsive meningoencephalitis do well with treatment with corticosteroids alone and many are eventually tapered off treatment with no recurrence. Recurrence however may be seen days, weeks, months or years after initial onset of clinical signs. Animals that have persistent neurologic signs despite high levels of corticosteroids and/or the prednisolone dose cannot be reduced to < 2mg/kg/day without relapse after several months of therapy, have a poorer long term prognosis.

Of animals that require high levels of corticosteroids for long periods to reduce their neurologic abnormalities the addition of cytarabine has helped in reducing the prednisolone dose required and a reasonable quality of life may be seen for months or >1 year.
Other idiopathic meningoencephalitides have been described in several small breeds including pug dog encephalitis, necrotising encephalitis of Yorkshire terriers (necrotizing leucoencephalitis), Chihuahuas and Maltese (necrotizing meningoencephalitis). Necrotising encephalitis may also be seen in other toy breeds. The histopathologic findings show extensive inflammation and predominantly cerebrocortical necrosis. The pattern of necrosis and cavitation of the brain parenchyma and presence or absence of meningeal lesions is often characteristic of these breed associated inflammatory diseases and the MRI findings closely mirror the histopathologic lesions at necropsy. The prognosis for all is very guarded. Treatment is as for GME although the response to treatment is often poorer.